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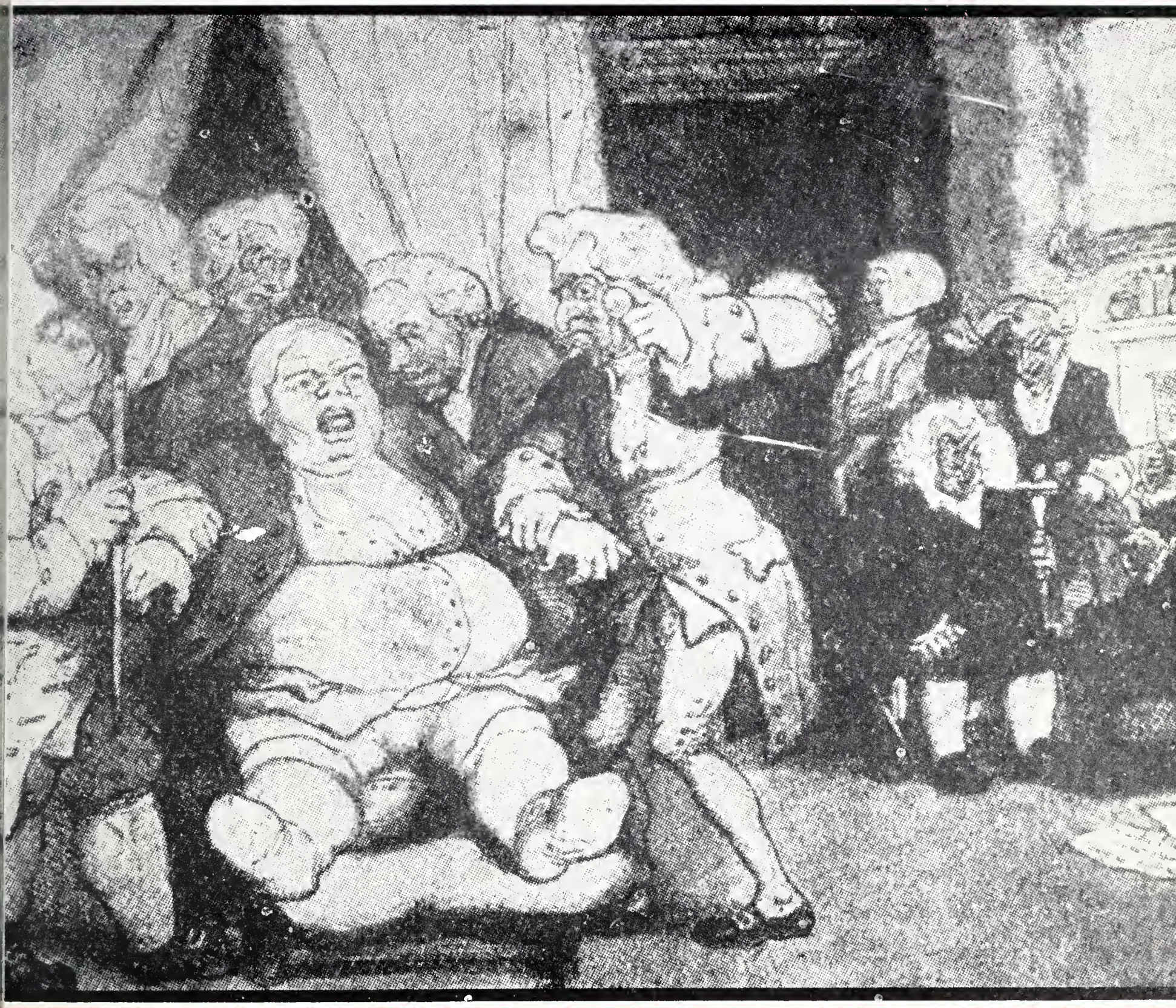

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VOLUME XXXIX

NUMBER 1

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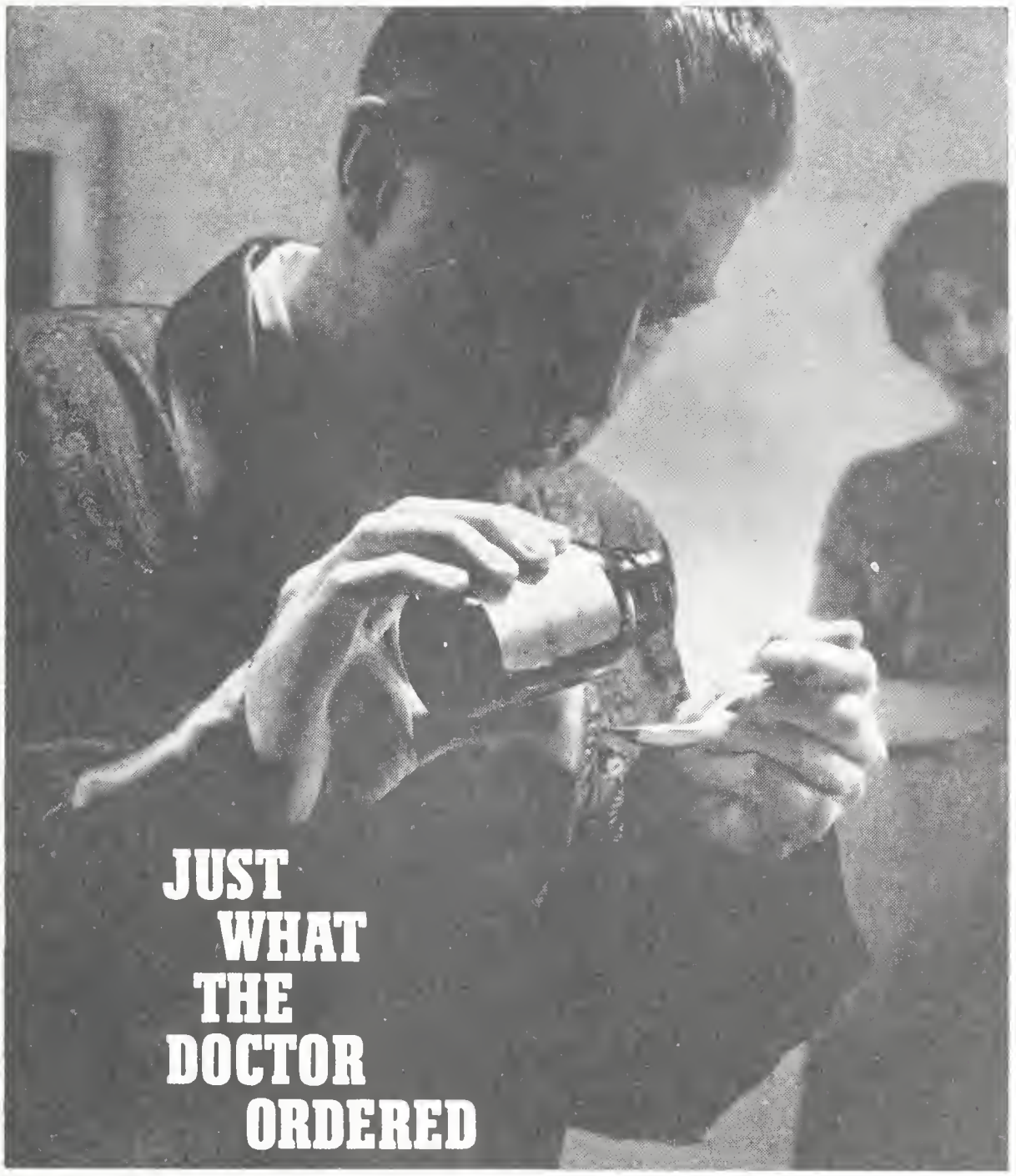

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THE COVER

Should this illustration have appeared as one of the photographs of our feature "On Inspection", it is certain that more than one of our astute undergraduate diagnosticians would designate the disease of the protagonist as 'nephrotic syndrome'. Such a diagnosis would be compatible with the opinion of the French artist who created this wood cut in the XVII century trying to depict a man suffering of kidney disease. We are inclined to disagree with the diagnosis. In view of the surroundings we favour 'obesity and acute alcoholic intoxication '.

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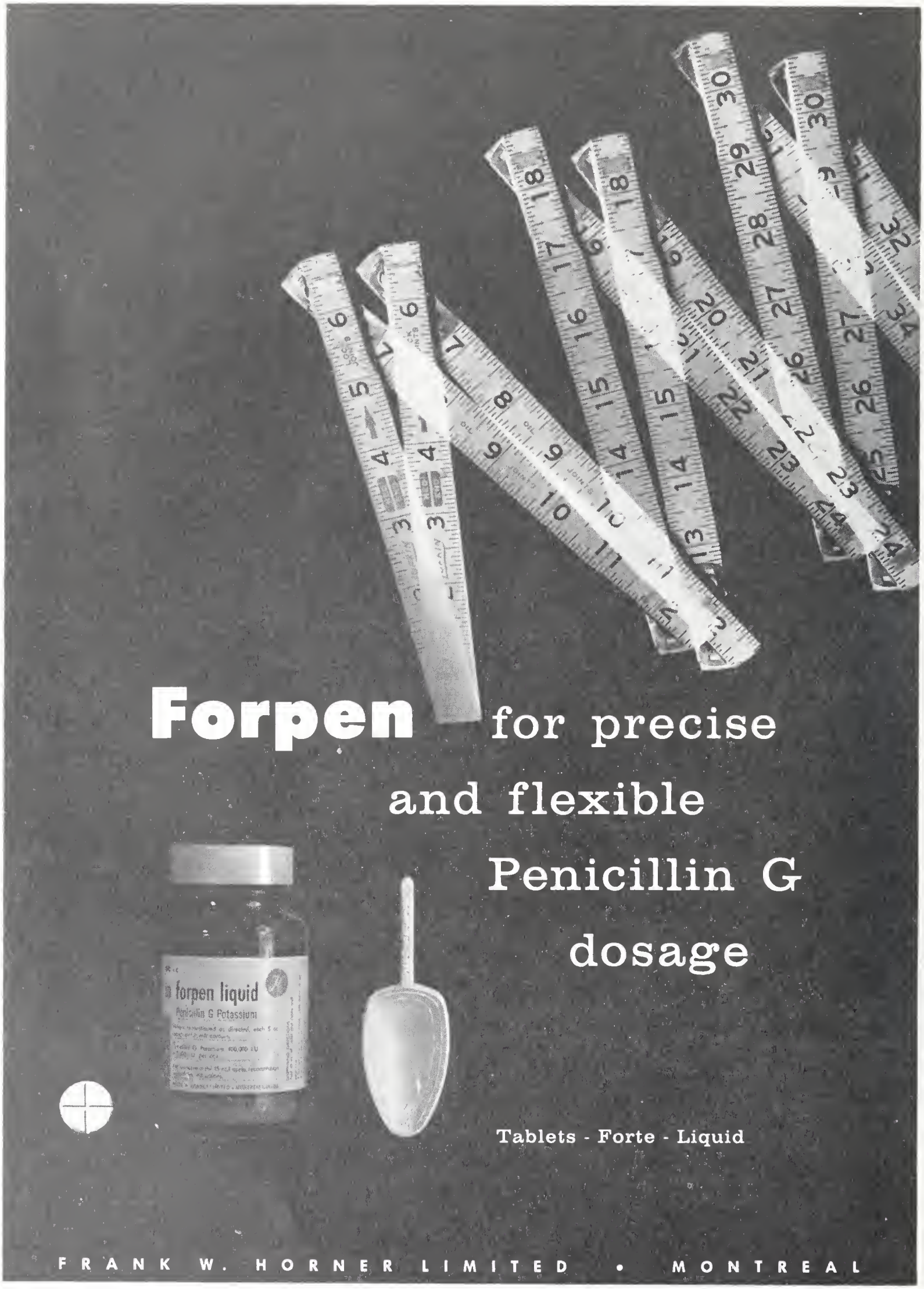
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Editorial

Medical Education

The recent decrease in numbers of applicants to the medical schools of this country in the presence of a serious shortage of doctors has made medical education one of the most important issues facing our profession to-day. Medical educators and medical students naturally feel that they are intimately involved in this controversial matter. Most of us (especially the students) feel sufficiently concerned about the situation to make hasty judgments either in defence or condemnation of the curricula and the organization of our Faculties of Medicine. Many of us (especially the medical educators) realize that the solution to the present problem requires more than mere changes of curricula and organization. Nevertheless, there is general agreement that some changes would be helpful but there seems to be general disagreement with respect to what changes should be made. We are concerned because the present situation appears to be leading to an *impasse* between wild-eyed rebels and stubborn reactionaries.

The undergraduate tends to be the wild-eyed rebel. The majority of undergraduate discussions on medical education, whether they be formal or informal, degenerate into a succession of vicious discourses attacking the *status quo*. We have nothing but contempt for such an attitude. There is a minority of students, however, that does not limit itself to attacks but goes to the extent of making constructive suggestions.

We wish to publish some of these opinions. The suggestions that follow are a summary of the ideas expressed by thoughtful undergraduates. They are not included in this editorial as an infallible remedy for all the evils that beset medical education but as a basis of discussion, especially for those medical educators whose decisions shape education policy.

"Let teaching interfere with my research? Hell, no. I just go in there impromptu, mumble a while and when they're all asleep, I sneak out."

from The New Physician, by permission

Curriculum. We know that the length of the medical course is the major deterrent for many brilliant high school graduates. The number of years involved results in a high total cost for the student, or his family, and this is a major deterrent for many other students who are interested in medicine. We feel that these two obstacles can be made to appear less formidable by altering the curriculum to a five year course with two years of compulsory internship (or three years with two years interneship for students having a bachelor's degree) and by making the final year of the five year course entirely free. We favour having the fees in the first four years increased by twenty-five per cent if necessary in order to make the final year devoid of cost to the student. One might just as well be dead for four years as in irreversible shock for five. These are the details of the proposed altered schedule:

Premedical course. We feel that the load in these two years should be increased to a level comparable to that in the medical years. If engineering students can complete heavy academic years immediately after high school, medical students can do likewise. We favour a thirty-two week scholastic year for premedical students divided into four terms.

We have good reason to believe that present policies for admission to premedical courses make it highly probable that many potentially good university students and

future doctors are being excluded because of poor adjustment to high school. We would like to see the standards for admission to Faculties lowered and the standards of first year premedical examinations raised considerably so that the student's performance in university will become the more important criterion for definitive acceptance to the Faculties of Medicine.

Medical course. We would like some humanities included in the curriculum of the professional years. Those interested in medical journalism sense the need for more training in English and Medical writing very acutely.

We find it necessary to propose five terms for the final year in medicine in order to include the subjects taught in the Specialties term of the present fourth medical year.

With the revised schedule, it would be desirable to have the universities grant the degree of Doctor of Medicine at the conclusion of the fifth year (third medical) and have the graduates write the Council examinations after completing one year of internship in a teaching hospital associated with the university from which they graduated. From then on, we do not see any need to change the present policies.

Suggested schedule:

I PREMEDICAL
- —English—3 terms (the entire course now taught in I Premedicine)
- —Zoology—4 terms (the entire course now taught in II Premedicine)
- —Inorganic Chem.—4 terms (the entire course now taught in I Premedicine)
- —Humanities I—3 terms (students' choice)
- —Physics—4 terms (the entire course now taught in I Premedicine)

II PREMEDICAL
- —English—2 terms (part of course now taught in II Premedicine)
- —Histology and Systemic Anatomy—3 terms (course taught in I Medicine plus one term of Systemic Anatomy)
- —Organic Chem.—4 terms (course now taught in II Premedicine)
- —Humanities II—3 terms (continuation of course begun in Premedicine)
- —Physiology—1 term (Respiratory and Cardiovascular systems)
- —Psychology—3 terms (entire course now taught in II Premedicine)
- —History of Medicine—2 terms (once weekly)

STUDENTS HAVING COMPLETED II PREMEDICINE	STUDENTS WITH B.A. DEGREES
I MEDICINE	
—Anatomy—4 terms (no change)	—Anatomy—4 terms (no change)
—Biochemistry—4 terms (no change)	—Biochemistry (no change)
—Physiology—3 terms (the balance of the course)	—Physiology—3 terms
—English—2 terms (once weekly)	—Histology—2 terms (course taken with II Premedicine)
—Humanities—2 terms (twice weekly—new course)	
II MEDICINE	—Physiology—1 term (course taken with II Premedicine)
—English (Medical Writing) —1 term (twice weekly)	—History of Medicine—2 terms (with II Premedicine)
—Humanities—2 terms (once weekly—continuation of course begun in I Medicine)	—Neuroan. and Neurophys.—2 terms
—Neuroanatomy and Neurophysiology —2 terms	—Pharmacology—4 terms
—Pharmacology—4 terms	—Pathology—4 terms
—Pathology—4 terms	—Medicine and Surgery (no change)
—Medicine and Surgery (no change)	—Bacteriology—3 terms
—Bacteriology—3 terms	—Public Health
—Public Health	

III MEDICINE
- —No changes except addition of a fifth term (Specialties) i.e. a 40 week academic year.
- —Final examinations: Mid-August

New Features

In addition to those already presented in this Journal during past years, we have added three new features. They are *Recent Advances, Interesting Cases* and *Clinical Pathological Conferences.* Some of these features will be included in each issue, others will appear less regularly.

Recent Advances, prepared by members of the Faculty of Medicine teaching staff, is an up to date report on current medical research. This feature was previously published by CAMSI, but will now be incorporated in the Journal.

Interesting Cases is a new idea. It will include case histories of patients seen in the course of their clinical work by second, third and fourth year students.

Clinical Pathological Conferences is a reproduction from *The New Physician,* a publication of the Student American Medical Association. We felt that the excellent quality and the didactic value of these *Conferences* would be an asset to our Journal and prove stimulating to the students of our Faculty.

In spite of the fact that two of these new features are not actually written by undergraduates, the greater part of the material printed in the Journal continues to be original work by members of the student body. Thus, we are not deviating from our long-established policy of being primarily a publication for student expression.

T.D.C.M.

New Subscribers

During the last four months our staff has had an experience that knows no precedent in the thirty-eight years of existence of our Journal. It was our happy task to process one hundred and seventy applications for new subscriptions. Most of these new subscribers are University of Toronto medical alumni or members of the teaching staff of our Faculty. The applications came from eleven different countries, ranging from Kano, Nigeria to Calcutta, India.

We wish to welcome our new readers. It is our hope that they will derive some benefit from our efforts and that we will have the advantage of receiving helpful criticism from them.

J.D.G.

ABSTRACT: *Folic Acid Therapy and Spinal Cord Degeneration in Pernicious Anaemia,* J. W. Baldwin and D. J. Dalesseio. New England Journal of Medicine, 264:1339.

It is an established fact that the administration of folic acid to a patient with pernicious anaemia will produce haematologic remission, but has no beneficial effects on the neurological manifestations. This article is concerned with the masking of pernicious anaemia by the administration of folic acid in multivitamin preparations or "shotgun therapy" given as treatment of anaemia and other diseases. Two such cases from the authors' own experience are presented, both with normal haematological pictures (including marrow), the findings of subacute combined degeneration and where the diagnosis of pernicious anaemia was confirmed by a Schilling test.

The authors outline the concept of the action of B_{12} and folic acid as coenzymes in synthesis of nucleoproteins. (Folic acid is necessary, for the synthesis of D.N.A., hence deficiency depresses mitosis while B_{12} is required in production of R.N.A. and D.N.A. Thus, deficiency of either cofactor depresses haemopoiesis while neural tissue, with minimal D.N.A. and high R.N.A. content requires B_{12} and derives no benefit from folic acid.) The administration of folic acid, by a mass action actually lowers serum B_{12} by diverting more of the available B_{12} for synthesis of D.N.A.

The use of multivitamin preparations containing folic acid is condemned because of the masking of haematologic manifestations of pernicious anaemia and consequent delay or failure of diagnosis.

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The Kidney Lesions of Diabetes Mellitus

By Charles F. T. Snelling, 6T2

In reading on this topic two points were constantly being focused. Firstly a myriad of lesions can be found in the kidney of a diabetic although only a few of these are considered unique to this condition. In this paper an attempt will be made to at least mention each possible discreet finding and the more important and controversial lesions will be dwelled upon. The second point concerns the ambiguity which now shrouds the names attached to glomerular lesions and is implied in associated syndromes. While there is no standard accepted authority on these, an attempt will be made to define these terms using criteria set out by well recognized authorities.

History

Until eleven years ago the Dewey Decimal System of library filing classified diabetes mellitus as a disease of the kidneys, since during the majority of the preceeding 18 centuries it was considered a primary disease of the urinary system. In the second century Aretaeus stated that diabetes was caused by something pernicious derived from the other diseases attacking bladder and kidney. Darwin in the early eighteen hundreds believed that diabetes was the result of the effect on the kidneys of prolonged alcoholic consumption. In addition he, observing that the urine of certain diabetics coagulated when heated, recognized the presence of protein. Armanni described hyalin vacuolization of renal tubules in 1875, and for the next sixty years the Armanni-Ebstein lesion or glycogen infiltration of renal tubules became the sine qua non of post-mortem diabetic manifestation in the kidney. The nodular form of intercapillary glomerulosclerosis was described in 1936 by Kimmelstiel and Wilson, marking the first occasion that the glomerulus had been incriminated in the diabetic process. Some investigators speculate that a failure to recognize this lesion previously is linked significantly to the commencement of insulin therapy a decade earlier. In addition to having diabetes and the nodular lesion many of Kimmelstiel and Wilson's original eight patients also exhibited oedema, hypertension, albuminuria and impaired renal function. Thus the nephrotic syndrome became associated with this nodular lesion, a partnership which has been the source of several subsequent investigations, reports and controversies as yet unsatisfactorily resolved at the present moment.

Review Material Data

The following article is based largely on the reports published by four groups of investigators and I will briefly describe each study series to be referred to. The Gellman (1) series consists of 63 renal biopsies on 53 diabetic patients with 9 subsequent autopsies. Gellman cautions that the incidence of renal lesions in his series is higher than in the normal diabetic population since patients handled by his team were referred to him because of renal complications. The Bucht (2) series was carried out on eight patients who had renal biopsies, plus a subsequent autopsy on one of these patients. The Farquhar (3) series was made on seven patients from which needle biopsy renal specimens were taken. The material of the two proceeding studies was taken from diabetic patients suspected of having renal disease and was observed both by light and electron microscope. The Smith (4) series is a review made in the Banting Institute of all the autopsies performed between 1925 and 1950 on patients dying in the Toronto General Hospital. Of 10,538 routine autopsies performed, 337 were on patients suffering from diabetes mellitus, an incidence of 3.1 percent. Of these 290 were suitable for study, of which 135 were male and 155 were female. The conditions reported in this series did not include all glomerular lesions recognized by other investigators but dealt with nodular glomerulosclerosis, glomerulofibrosis, crescentic exudates or fibrin cap and capsular lesions or capsular drop. The preceding information should be considered in weighing the significance of the following reported findings. In addition specific references are made to other workers indicated in the bibliography. My personal research in this field is confined to a perusal of the printed word. Essentially this topic is a study in pathology with clinical and functional considerations to be touched on briefly.

Glomerular Lesions

Diffuse Diabetic Glomerulosclerosis

Whether this lesion in fact is pathognomonic of diabetic nephropathy or is merely either an arteriosclerotic non-specific change or arteriolar

nephrosclerosis is a point of contention frequently encountered in this field. Gellman offers a valid defense on the lesion and his arguments will be offered later. In his series 75 per cent of the biopsy specimens and all autopsy cases demonstrated this process. Regarding the diffuse variety as lacking good diagnostic criteria it was not studied in Smith's Toronto series.

Histologically under the light microscope one sees P.A.S. positively stained material in the glomerular capillary walls which are uniformly thickened. This material, shown by special staining to contain lipid, mucopolysaccharides and haemoglobin but no reticulin fibres, is present around the full circumference of the capillary wall, giving on cross-section the appearance of a thickened ring. In contrast the nodular process involves the side of the capillary wall closest to the hilum leaving the portion facing the Bowman's capsule thin and delicate until the capillary has been completely occluded. The diffuse thickening involves first the peripheral loops at an early stage but soon affects all loops of a given glomerulus although not necessarily to the same degree. Eventually the entire capillary lumen is squeezed shut by this annular process, which then appears to spread from the basement membrane to involve the endothelial cells, destroying these as well as later affecting the epithelial cells, sparing only the nucleus.

Bell (5) has indicated that nodular lesions are never seen in a given kidney unless accompanied by diffuse lesions, while diffuse manifestations may exist alone and proceed to complete glomerular obliteration without nodule formation. Therefore he concluded that nodular glomerulosclerosis was preceded by and developed from diffuse glomerulosclerosis without a clear cut delineation, a point which may be questioned on the basis of the following findings as well as electron microscopic observations to be described later. Gellman *et al* (1) agreed that nodular lesions were never seen in the absence of the diffuse process. No correlation appeared to exist between the severity of the two lesions. Diffuse glomerulosclerosis always involved the peripheral capillary loops first while often in the presence of large nodules this rim of capillaries remained untouched. The nodules contained reticulin fibres never seen in the most advanced diffuse process. The nuclei were seen on the periphery of a nodule whereas they were buried uniformly throughout the diffuse lesion.

To distinguish diffuse diabetic glomerulosclerosis from membranous nephritis the following criterion should be observed. (1, 6) The membranous process seems to involve all capillaries of all glomeruli of the kidney equally from the onset. In contrast a great variation in the thickness of individual capillary walls, well described as local and focal is observed both in the individual glomerulus where the peripheral capillaries are first involved, and on a consensus of all glomeruli seen on a slide. Membranous lesions are not commonly accompanied by arteriolosclerotic changes until late in their process when hypertension is present while diffuse diabetic glomerulosclerosis is almost always coupled with arteriolosclerosis. The endothelial cell nuclei are on the luminal side of the thickened capillary walls while in the diabetic process the nucleus appears to be buried from an early stage in the thickened wall. Later the epithelial nuclei also seem embedded.

A somewhat more subtle list of differentiations exists between diffuse diabetic glomerulosclerosis and the glomerular lesion of arteriolar nephrosclerosis. The diffuse process commences in the periphery of the glomerulus not at the hilus. The fibrillar appearance suggesting splitting of the basement membrane is not seen as in arteriolar nephrosclerosis. When completely involved with the diabetic lesion the glomerulus retains its normal size instead of shrinking. The thickened ring does not contain collagen.

Nodular Diabetic Glomerulosclerosis

This is the lesion described by Kimmelstiel and Wilson (12) bearing their names and also known as intercapillary glomerulosclerosis. This lesion is probably that most specific for diabetes mellitus although it is not always present. In the Toronto series 12.7 percent of kidneys examined demonstrated this lesion, while Robbins reports fifteen percent and Harrison 65 percent. In the Gellman (1) series one-half the renal biopsies and all but one autopsy specimen demonstrated the presence of the nodular lesion. In a series done on kidneys of diabetics whose disease was secondary to hemochromatosis Lonergan and Robbins (7) were unable to observe a single nodule. In light of the fact that clinical evidence of diabetes mellitus may disappear with the onset of intercapillary glomerulosclerosis and development of renal failure, this lesion may appear to be present in a non-diabetic.

The nodular lesion under the light microscope is characterized by a spherical deposit of homogeneous, hyalin-like, acidophilic material in the periphery of the glomerular tuft, apparently surrounded by cross-sections of patent capillary loops.

Since one is confused easily by the name intercapillary glomerulosclerosis, an attempt will be made to explain its meaning. On close examination of the juxtacapsular portion of a nodule one sees ringlets of capillaries, present all around this border of the globular mass. These are either cross-sections cut through one or several capillaries lying on the outside surface of the nodule. Whether these masses lie within the endothelial cell cytoplasm of the glomerular capillaries and are thus intra capillary or lie outside the endothelial cell membrane, in a space created between the basement membrane and the endothelial cell membrane and are extracapillary is too minute for the power of the light microscope. This position is a hotly debated point amongst electron microscopists whose arguments follow. The nodule is likely composed of a mucopolysaccharide with low protein and high carbohydrate content, demonstrating reticulin fibres with special stain and likely deposited from the blood. This is the lesion Kimmelstiel and Wilson described. Perhaps incorrectly the Kimmelstiel-Wilson nodular lesion has subsequently become associated with other glomerular lesions and the Kimmelstiel-Wilson syndrome which by further investigation has been shown to correlate poorly with the presence of the Kimmelstiel-Wilson nodule and correlate well with the presence of the diffuse lesion.

Electron Microscope Findings

Bergstrand and Bucht in Sweden and Farquhar in Boston simultaneously have studied the diabetic glomerulus under the electron microscope and have published comprehensive illustrated reports of their findings.

Both groups of authors agree that the diffuse lesion represents a two to six fold thickening of the basement membrane. Farquhar believes this thickening occurs through deposition of hyalin-like material between the basement membrane and the endothelial cell membrane. She explains the transition from the initial diffuse lesion to the nodular lesion which she believes to be a progressive single process. Bergstrand and Bucht believe that the thickening of the basement membrane is an intrinsic metabolic change in which the depolymerization of polysaccharides results in thickening, thus increasing resistance to glomerular filtration which is effected through the substance of the basement membrane. They envision pores across the basement membrane existing between fine filaments of molecular chains. A metabolic change produced in diabetes mellitus results in increased distance between some or all of these filaments thus admitting protein molecules which normally do not fit into the pores. Thus they explain both decreased filtration and proteinuria seen with diffuse diabetic glomerulosclerosis.

The genesis and position of the nodular lesion is described in two widely differing fashions. Farquhar and associates describe it as a progression of the diffuse process in which increasing amounts of hyalin in and about the basement membrane push the capillary endothelial cells ahead of them towards Bowman's capsule and later expand so as to encroach upon and obliterate the capillary lumen, separating it from the endothelial cell nucleus without actually entering into the cytoplasm of the endothelial cell proper. They stated that in their electron microphotographs they could see endothelial cell membrane separating the endothelial cell nuclei and cytoplasm from the hyalin material, indicating that this hyalin remained extra endothelially. On observation of the photographs it did not appear that the endothelial cell membrane divided hyalin from nucleus and cytoplasm, but rather, it appeared that the hyalin masses were in fact mixed up intimately with endothelial cell cytoplasm. Bergstrand and Bucht demonstrated a new substance, a so called hyalin band lying between the thickened basement membrane and the endothelial cell membrane and differing in minute structure from the basement membrane in that it contained fibrils which could not be demonstrated in basement membrane. This substance they claim is secreted by the endothelial cell and is closely allied to the endothelial cell membrane while it is often widely separated from the basement membrane. The nodular lesion begins as the hyalin band, the material of which is invaginated into the cytoplasm of the endothelial cell, splitting the cytoplasm into several connecting islets. As the hyalin increases the cytoplasm decreases, the cells die and large intracapillary hyalin masses are formed. In serial sections one sees connection between the intracellular masses and hyalin band while in adjoining sections the hyalin masses are isolated and separated from the hyalin band by a clearly visible endothelial cell membrane. One is inclined to support Bergstrand and Bucht's observations following careful scrutiny of both sets of photographs which are suprisingly similar, differing only in the attached descriptions. The important point to note is that the position of the nodular lesion in respect to the capillary endothelial cell is still undetermined.

Association of Lesions with Clinical Findings

In the Gellman series fourteen patients had the nephrotic syndrome, characterized by proteinuria,

hypoalbuminaemia, hypercholesterolemia and oedema. Compared with patients who did not have the nephrotic syndrome no correlation existed between the duration of diabetes and appearance of the nephrotic syndrome although figures suggested that juvenile onset diabetics were especially liable to develop the syndrome. A good positive correlation existed between the severity of diffuse glomerulosclerosis and presence of nephrotic syndrome but not with the severe nodular lesion. Sometimes no nodules were found in the presence of nephrotic syndrome while the diffuse lesion was always demonstrated.

Presence of diffuse and nodular lesions was related to the duration of the diabetes. The nodular lesion was associated with an increased incidence of ketosis, diabetic retinopathy, oedema and nephrotic syndrome but the incidence of these was not correlated with the severity of the nodular process. In contrast the more severe the diffuse lesion, the more pronounced were the following entities, namely: increased diastolic blood pressure, proteinuria, increased B.U.N. and serum creatinine, hypoalbuminemia, decreased urea and creatinine clearances and oedema and nephrotic syndrome. Thus it might be concluded that the nodular lesion while diagnostically important has questionable functional significance. In conclusion the nephrotic syndrome and renal failure are not caused by the Kimmelstiel-Wilson nodular lesion and hence the nephrotic syndrome and associated entities should not be called the Kimmelstiel-Wilson syndrome. (1)

Exudative Lesions

Two types of lesions are included under this heading, both having been described by Barrie, Aszkonazy and Smith of Toronto (13). The fibrin cap was found in approximately five percent of the Smith series. It is a crescentic fibrin-like cap of eosinophilic material located on the convex outer surface of the renal glomerular tufts, lying between the basement membrane and the endothelial cell membrane. It was not necessarily associated with the presence of the nodular lesion but was always accompanied by severe arteriolosclerosis. The capsular drop is a fibrin like lesion found in the concavity of the parietal portion of Bowman's capsule, lying between the epithelium and basement membrane of the capsule. This lesion may differ from the fibrin cap in that it becomes rapidly organized into fibrous tissue. In some cases these exudates have been observed lying free in the capsular space, but serial sections reveal their attachment to the fibrin cap. Gellman *et al* (1) feel that these two lesions are manifestations of the same process and are found in conjunction with nodular and diffuse lesions accompanied by severe vascular disease. Hall (9) believes that the exudative lesion is due to ischaemia associated with narrowing of the renal artery or its branches by atherosclerosis. The exudative lesion is always accompanied by hyalin changes in the extra glomerular arterioles.

Capillary Aneurisms

In early diabetic glomerulonephropathy before glomerulosclerosis is present, the glomeruli are congested with blood and the capillary loops dilated. With the onset of the diffuse lesion, most of the capillaries become narrowed but the occasional one remains dilated and becomes an aneurism. Capillary aneurisms with hyalin capping bearing Ballantyne's name are also seen in the retina. There seems to be a strong correlation between the presence of these retinal capillary aneurisms and nodular glomerular lesions (10) in the same patient.

Lipophages

Gellman recognized large, vacuolated cells containing fat in one-third of his specimens. These cells may be circulating and impacted in the glomerular capillaries, or endothelial cells which have imbided fat.

Ischaemia and Hyalinization

Regardless of whether the diffuse or nodular lesion is the precursor complete hyalinization of glomeruli is observed. The older lesions stain in such a way that suggests replacement of the polysaccharide complex by fibrous tissue.

Tubular Lesions

Tubular degeneration of two types is seen. The Armanni-Ebstein lesion resulting from glycogen infiltration of renal tubules used to be the most common post-mortem finding in the diabetic kidney before the use of insulin. It is characterized by a large clear cell with an intact isolated central nucleus. Today it is rarely seen.

Fatty degeneration of the proximal convoluted tubule is associated with lack of diabetic control and is seen in patients dying of diabetic coma. This nonspecific lesion is also seen in shock and diffuse glomerulonephritis.

Atrophy and dilation of tubular cells appears to be a sequel to glomerular lesions.

Peritubular hyalin cuffing with an eosinophilic material similar to the hyalin-fibrinoid substance of the glomerular exudative lesion is found. This cuffing of renal tubules is similar to cuffing of acinar ducts of diabetic women.

Vascular Lesions

Severe atheroma of the larger renal arteries and intrarenal arteries is highly characteristic of diabetes. This is likely related to the diabetic tendency for generalized arteriosclerotic changes. Both Hall (9) and Gellman (1) believe that atherosclerotic plaques and lipophages in the walls of the parenchymal branches of the renal artery are pathognomonic of diabetes.

Arteriolosclerosis of glomerular arterioles seems to be more severe than that observed in any other condition. The glomerular lesions are always present in the diabetic before the arteriolosclerosis occurs, suggesting that the appearance of the intercapillary glomerulosclerosis predisposes to and accelerates the appearance of the vascular change (11), rather than the reverse. In non diabetics arteriolosclerosis is never accompanied by intercapillary glomerulosclerosis.

Smith (4) calls the intraglomerular arteriosclerotic lesion glomerulofibrosis. This process consists of thickening of the axial connective tissue of the glomerular tuft with little basement membrane change. This lesion he observed in 43 percent of his autopsies, the highest frequency of any glomerular lesion he observed. Two-thirds of kidneys exhibiting this process possessed extraglomerular arteriolosclerosis as well.

Parenchymal Lesions

Pyelonephritis is probably the renal lesion observed most frequently today in the kidneys of diabetics, who are more susceptible to infections of all kinds than the population in general. Since pure pyelonephritis in diabetes does not differ from pyelonephritis observed in other patients it will not be enlarged upon.

Papillitis necroticans is an interesting variant of pyelonephritis. It occurs secondarily to acute pyelonephritis. Grossly there is necrosis of the tips of renal papillae with a narrow zone of hyperemia in the line between viable and necrotic tissue. Microscopically one sees coagulative infarct necrosis with preservation of tubular outlines, devoid of nuclei and no leucocytic infiltration save in the junctional hyperemic zone. Nests of proliferating bacteria are found in the necrotic area but are not accompanied by an inflammatory cell response attesting to the absence of blood supply. Vasculitis and thrombosis of the branches of the arcuate arteries which supply the pyramid may be visible in the hyperemic zone. These necrotic papillae are sloughed off and their passage along the ureter is sometimes accompanied by renal colic.

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THE SANGUINE

THE PHLEGMATIC

THEY ALL SUBSCRIBE TO THE UNIVERSITY OF TORONTO MEDICAL JOURNAL

THE CHOLERIC

THE MELANCHOLIC

THE FOUR TEMPERAMENTS (Hippocrates)—from a Zurich manuscript of 15th century

Extracorporeal Dialysis by use of the Artificial Kidney

By P. A. Korhonen 6T2

An artificial kidney consists of an apparatus through which waste products, electrolytes, or other endogenous or exogenous substances in the blood, are regulated by diffusion across a differentially permeable membrane into a controlled bath. This process is called haemodialysis. Since this is done by an apparatus outside the body it is called extracorporeal haemodialysis to differentiate it from intracorporeal haemodialysis by means of peritoneal lavage, intestinal lavage or intestinal ion-exchange resin.

It is to be emphasized that this article does not attempt to deal with the management of the disorders of kidney function but only in the use of the artificial kidney as an adjunct to conservative treatment.

Principle

The principle is a simple one. Blood is led from an artery or vein through a cellophane tubing which is immersed in a bath of a suitably prepared solution. The blood is then returned to the patient by a venous cannula.

The bath consists of a large volume of water in which sodium, potassium, calcium, magnesium, chloride and bicarbonate are dissolved in physiological concentrations with glucose added to bring the osmotic pressure of the fluid to that of the plasma. The pH is adjusted with lactic acid and 10% carbon dioxide in oxygen which is bubbled through the bath fluid to maintain the pH at 7.4. The fluid is kept at 37°C to 40°C by a heater and thermostat. After the cellophane coil is "primed" with fresh heparinized compatible blood, the patient's blood is also heparinized before the apparatus is connected to the arterial and venous cannulae.

During dialysis an exchange of small molecules takes place across the cellophane membrane, depending on the relative concentrations on either side. Thus the initial high concentration of urea in the blood and the absence of urea in the bath leads to a rapid clearance of urea from the blood to the bath. Similarly, a high blood potassium level is lowered. If one wishes to remove potassium more rapidly in cases of severe hyperkalaemia, potassium may be omitted from the bath for the first hour and then be added in normal concentrations. Large molecules such as plasma proteins cannot penetrate the membrane nor can particles as large as viruses or bacteria, so that absolute sterility of the bath fluid is not required. During dialysis, eliminated substances accumulate in the bath fluid. Since the original physiological salt concentrations are altered, the bath must be drained and filled with freshly prepared solution about every two hours. The total dialysis time is usually about six hours exclusive of the time required for cannulation and preparation.

Some attention should be paid to the osmolarity of the blood and bath. If this is considerably higher in the blood than in the bath, movement of water from the bath to the blood may occur resulting in overhydration of the patient. Substances such as various polysaccharides and colloids as well as high concentrations of glucose have been used to increase the osmolarity of the bath. Another and more effective method of preventing the influx of water is by ultrafiltration. Here, by decreasing the hydrostatic pressure of the bath or by increasing the hydrostatic pressure of the blood, it is possible to counteract the osmotic pressure of the blood, even to cause the passage of large amounts of ultrafiltrate from the blood. Lately, several centres have successfully treated acute pulmonary oedema (1) and congestive heart failure by the use of the artificial kidney with ultrafiltration.

Potentialities

Firstly, the artificial kidney can bring down the blood level and total body content of urea and other diffusible nitrogenous and non-nitrogenous products of metabolism. Urea itself is relatively non-toxic but there are many toxic substances, many of unknown chemical composition which accumulate in uremic patients and which are presumably removed during dialysis.

A second important function of the apparatus is to restore the patient's electrolyte pattern to normal state in particular, a dangerously high potassium level can be lowered, and a dangerously low alkali reserve raised. In addition, some models can remove water.

A third function is to remove exogenous toxic substances in acute poisoning such as salicylates, barbiturates, and other drugs.

Development

The first successful "artificial kidney" used with animals was developed by Abel *et al* in 1914. It consisted of colloidin as the membrane and hirudin extracted from leeches as the anticoagulant. (2) Haas in 1923 employed a similar apparatus in experiments with human beings. Further experimentation in dogs was done by Thalhimer in 1938 where he introduced cellophane and heparin but, unfortunately, he did not complete his work. (3)

The first artificial kidney to have any clinical success was developed by Kolff in 1944 in Holland. (4) His kidney consisted of cellophane tubing wound around a horizontally placed drum which rotated half immersed in the bath fluid. (5) Alwall in Sweden and Murray in Canada (6), working independently, described dialyzers in which the cellophane tube was wound around a vertical stationary drum made from steel mesh. (7) The bath fluid passed upward past the cellophane tubing. These artificial kidneys had the advantage of being capable of ultrafiltration.

Another type of apparatus was developed by Skeggs and Leonard in 1948. The blood flowed between two flat sheets of cellophane which were in turn compressed by two corrugated rubber pads. (8) The bath fluid flowed in these corrugations.

All the kidneys developed to that date had several disadvantages. They were difficult to assemble and sterilize. Some of the parts in contact with the blood were used repeatedly which led to contamination with blood proteins leading to pyrogenic reactions. Most of these problems were eliminated in the *Disposable Twin Coil Kidney* developed by Kolff in 1956 in Cleveland. Two parallel tubes of cellophane placed between fibreglass screens were wound concentrically inside a tin can. (9) Siliconed inlet and outlet cannulae were connected to the cellophane tubing, whereupon the coil and cannulae were sealed inside the tin container. This unit was then autoclaved. For use, the arterial plastic tubing was put through a sigmamotor pump and thus the blood never left the tubing. After use, the whole sterile unit was discarded. This type of kidney is now the most popular artificial kidney in use.

Cases For Dialysis

Potential cases for dialysis may be classified into four broad groups, but it is often difficult to allocate individual cases immediately to the correct group, and the final grouping may be impossible during life.

The first and ideal group are those with acute renal failure due to reversible lesions. Where there has been a clearcut incident of a type liable to this group, classification of the case is easy. However, many cases present difficult and confused clinical pictures, many of which unfortunately prove to fall into the second group of acute irreversible renal failure. Here, dialysis is of only temporary benefit, but many such cases require to be dialysed if only to give the patients the benefit of the doubt, and to allow time for further attempts at diagnosis and treatment.

The third group consists of patients with chronic renal lesions. Here the diagnosis appears to be easy but it is not always the case. Dialysis, according to some centres, is justified if the progress of the disease is slow, if a long remission can be attained, or if deterioration has occurred as a result of some reversible incident such as an infection or an episode of dehydration. Some centres dialyse prior to a necessary surgical operation especially if it involves the urinary tract. (10)

The fourth group consists of cases of acute intoxication by various exogenous poisons. (11) Many drugs which are ingested in toxic quantities, either accidentally or with suicidal intent, are diffusible through the cellophane membrane and thus are susceptible to removal by the artificial kidney. Many drugs, such as barbiturates, salicylates, glutethimide (Doriden), and streptomycin, have been removed. (12) Bromide intoxication has also been treated in this fashion. (13) (14) (15)

The artificial kidney has been used to remove ammonia in hepatic coma. (16) (17) However, the benefits have only been temporary.

Indications For Dialysis

Indications for dialysis vary with the opinion of different groups of experts but the following are the most universally accepted:

Clinical Deterioration. In this category mental changes such as mental retardation or developing uncooperation and persistent nausea or vomiting, or inability to cough and clear chest secretions well, are important signs. Most centres recommend dialysing before the onset of convulsions, semi-

coma, severe mental confusion or uremic hypotension.

Blood Urea Nitrogen Over 180mg. per 100 ML. This is important not because of any toxic property of urea, but because the rate of rise of the level is indicative of the rate of protein breakdown.

Serum Potassium Over 7m Eq. Per Litre. This is an urgent indication particularly if the rise is progressive and fails to respond rapidly to treatment with ion exchange resins, or other conservative means.

Alkali Reserve Below 12m Eq. Per Litre.

Overhydration. This may be a factor in general deterioration and occasionally a large factor in cases where the onset of oliguria has been insidious and the diagnosis has been delayed.

Acute Poisoning. Some centres recommend dialysis in certain cases of poisoning before permanent damage has taken place.

Dialysis should be elective, not an emergency procedure. Potential cases should be referred to a dialysis centre early in the course of their illness. Immediate transfer may not be necessary but it is valuable to have discussed conservative treatment with the dialysis specialist and to inform him of a possible dialysis early.

Contraindications

Since the patient must be heparinized to prevent coagulation of blood within the artificial kidney, bleeding (particularly into the central nervous system and gastrointestinal tract) is a contraindication. Further exploration of "regional heparinization" may eliminate this objection. Such a method would make it possible to heparinize blood as it enters the artificial kidney, and to neutralize it with protamine as it emerges from the distal end of the apparatus. (18)

Recent myocardial infarction and hypotension are not only contraindications but they render the procedure more difficult. It is, however, possible to pass a cannula through the saphenous or femoral vein to the inferior vena cava so that adequate arterial pressure is not always a prerequisite for adequate flow. (19)

Conclusion

The artificial kidney, in any one of the present day forms, can be an efficient and safe device for the correction of abnormalities of extracellular fluid composition where these abnormalities are due to substances which diffuse readily through a cellophane membrane. In so far as these abnormalities renders the patient less able to tolerate his illness, the removal of such by the artificial kidney may be clinically useful. Frequently, however, the patient is ill for multiple reasons, many of which are not amenable to haemodialysis. The physician confronted with such cases must have wide experience not only in the use of the artificial kidney, but also in all possible concurrent disease processes, so that he may be able to select wisely the instances where dialysis may be of benefit.

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CIBA

PRESENTS

ON INSPECTION

Fig. 1. —

What is the mass at the base of this young girl's tongue? What are the symptoms, treatment, and chief complication of treatment of this defect?

J. BREBNER, 6T2

R. S. GILDER, B.A.

Fig. 2. —

This middle-aged male suffered a spontaneous pneumothorax ten years ago. Two years ago, an enlarged node in his left supraclavicular region was discovered, and a course of therapy instituted. The disease never has been completely under control.

One month ago, his symptoms were: strength and energy good, occasional night sweats but no feverishness otherwise, no respiratory or gastrointestinal symptoms, but marked swelling of left arm and hand with limitation of abduction of the left shoulder.

On examination — Small, discrete, freely mobile glands were found in the right tonsillar and supraclavicular areas. A firm indiscrete mass of 5 cm. diameter, with overlying ulcerated skin of 3 cm. diameter, was present in the left supraclavicular region. Massive left axillary involvement with marked oedema of the left arm and dilatation of superficial veins was present. There was a tumour mass, 9 cm. by 4 cm., lying in the left chest wall at the posterior axillary line, and another more diffuse mass overlying the left scapula. There were no inguinal nor epitrochlear glands palpable. Trachea was central, blood pressure and pulse normal, liver and spleen not palpable, and there were no abdominal masses.

What is your diagnoses?

Fig. 3. — Name the disease process.

Fig. 4. — This patient has sweating, only on the left side of his face. What is the syndrome this case represents? What are the possible causative factors?

Fig. 5. — What disease does this classically appear to represent? Now, what syndrome does this picture conjure up to mind when linked to a story of febrile migratory polyarthritis, splenomegaly, and leukopaenia?

ANSWERS
MAY BE
FOUND ON
PAGE 54

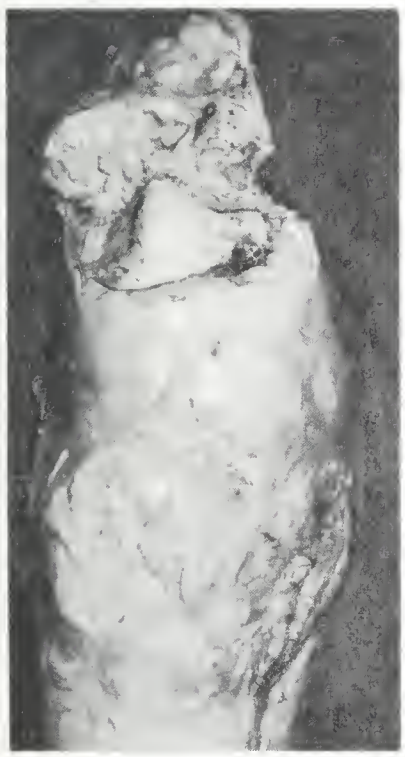
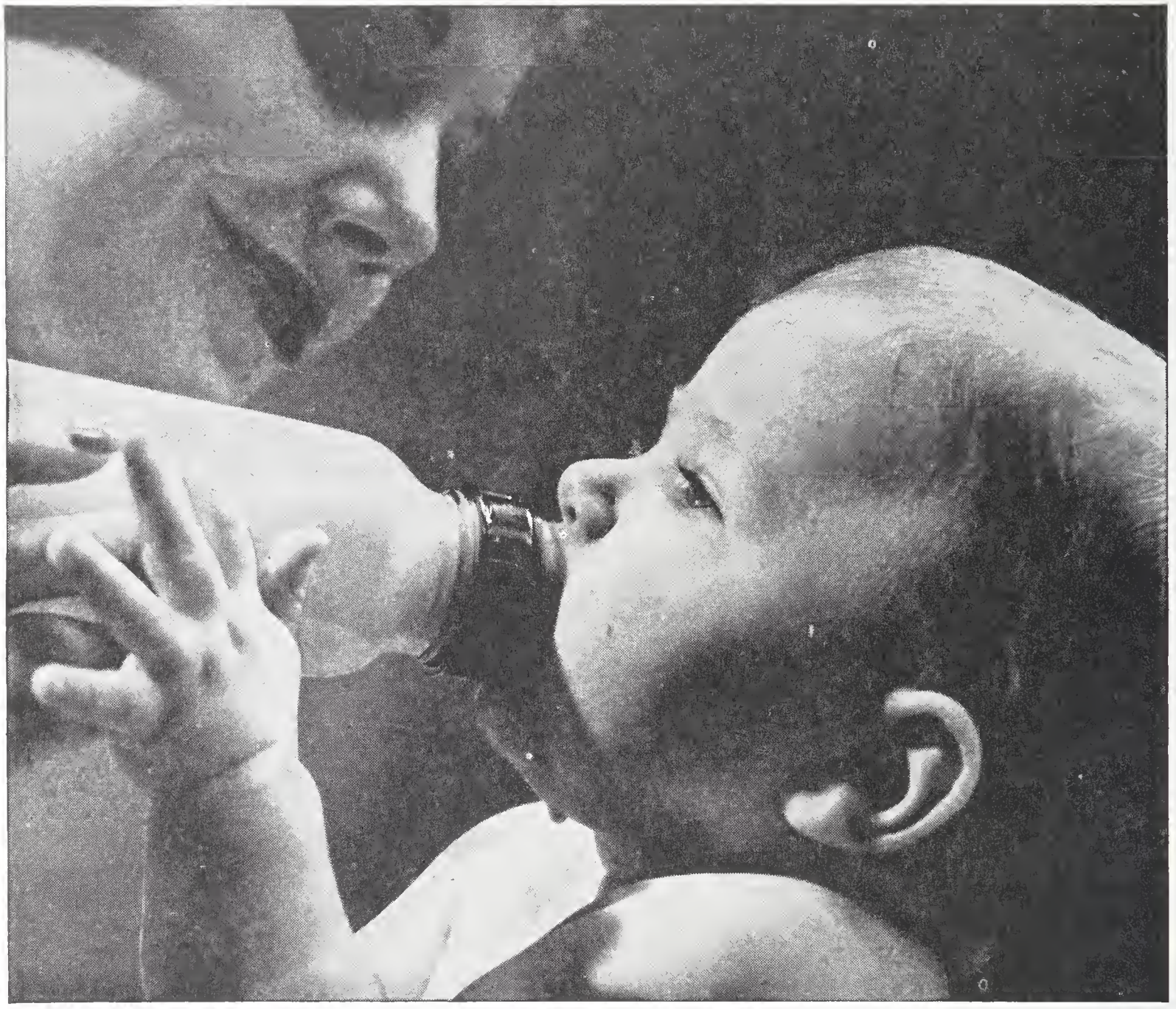


Fig. 6. and Fig.7. — Special case.

Picture number six is of the knee joint and proximal end of tibia, and number seven is of the cranium; both taken at the autopsy of a teen-age male. The predominant symptom over two years was pain.

What are your differential and provisional diagnoses of this lesion?



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CANADA'S PREMIUM INFANT FORMULA MILKS

Peritoneal Lavage and Ion Exchange Resins

David Cole 6T2

The kidney functions as a clearing-house of wastes and poisons and in certain states, where this function is deranged, toxic concentrations of metabolites and ingested substances accumulate. Thus, a patient in acute or chronic renal failure demonstrates a rise in the level of urea nitrogen in the blood.

The treatment of these states, then, is directed at minimizing this toxic buildup. The insertion of an extracorporeal dialysis apparatus, or artificial kidney, into the circulation in such circumstances may be life-saving, by removal of these substances from the extra-cellular fluid compartment. The techniques of peritoneal lavage and cation exchange resins, while not dramatic, are considerably simpler and hence more suitable for widespread application.

Peritoneal Lavage

The peritoneum is a semipermeable membrane with a surface area of about 22,000 square centimetres, comparable to that of the kidney glomeruli. By peritoneal lavage, the dialysing potential of this membrane is activated, rendering it an excretory organ. A solution is instilled into the peritoneal cavity and solutes and water cross the membrane according to its permeability and to the respective osmotic gradients between the dialysing fluid and the plasma.

This technique was applied as a substitute for the failing kidney in man as early as 1923 with success in lowering serum potassium, but the continuous bathing of the peritoneum resulted in many problems, the chief of which was peritonitis. In fact, one paper reflected the prevailing attitude in 1948 by stating that "The continuing hazard of peritonitis makes it necessary to regard the method as still in the experimental stages, and it should not be considered for routine clinical use." Interestingly, the infecting organisms (generally B. coli) are thought to arise not from contamination of the apparatus or incisions but rather from the contents of an irritated, hyperpermeable intestine. Frank *et al* concluded that the only measure which would render the technique safe enough to be therapeutically valuable was the development and use of a new antibiotic to combat the infection.

However, the introduction of an intermittent lavage technique in 1951 offered more hopeful prospects. By instilling a certain volume of dialysis fluid into the peritoneal cavity of nephrectomized dogs, leaving it there a certain time to allow exchange of diffusable wastes and extracting the fluid plus wastes subsequently, the dogs were maintained for an unprecedented time (longer than possible with the artificial kidney) and eventually died of malignant hypertension. In other words, the excretory functions of their kidneys appeared to have been adequately replaced by the dialysis.

This intermittent procedure involves only one incision, through which the dialysing solution is instilled, and later removed. Not only does this allow a closed system with to and fro flow (with less opportunity for contamination) but it permits the use of simpler equipment and less skilled management than does the continuous method. Nearly all subsequent applications of peritoneal lavage have been by the intermittent method.

The composition of the dialysing fluid approximates that of normal extra-cellular fluid with respect to individual electrolyte concentrations, pH, and osmolality. The composition of the fluid and the time allowed for diffusion across the peritoneum are the two important variables in the procedure, and are adjusted to determine 'how much of what' is removed from (or added to) the patient's extra-cellular fluid.

In renal shutdown, one of the most important and toxic substances which accumulates is potassium. Hence, in this condition, the fluid is made up potassium-free. However in other non-oliguric states where potassium retention is not a problem, potassium chloride is included in the solution. The osmolality of the solution must be adjusted, since the protein content of plasma would tend to absorb water and overhydrate the oliguric patient disastrously if no provision were made to prevent such absorption. This is done by adding dextrose to adjust the osmolality. Although the peritoneum is permeable to glucose, the diffusion of the sugar molecules across the membrane is much slower than that of water. Hence, a hypertonic glucose solution will tend at first to dehydrate the patient. Later, equilibrium is established, the transfer is reversed, and water is reabsorbed. It is important to allow enough time to achieve extraction, but not enough for absorption. Grollman found that there is no change in the peritoneum's

permeability to glucose during the procedure (it was feared that irritation would cause fibrinous exudate on the peritoneum, interfering with diffusion) and that a 2% solution of dextrose would maintain the transfer of fluid from extra-cellular fluid to dialysing solution for six hours. A two-hour period has been found adequate for achievement of equilibrium with respect to electrolytes, urea, creatinine and NPN. Hence, this is a fairly standard duration for individual episodes of peritoneal dialysis. It has been found that two litres is about the optimum volume for instillation in the average-sized patient, and the procedure may be repeated *ad lib* guided by the patient's condition.

The procedure is simple and the complications are relatively few. The inclusion of heparin in the fluid and the use of a non-irritating plastic catheter for its instillation and withdrawal have reduced the hazards of fibrin plugging the catheter and interfering with peritoneal permeability. The intermittent technique, with less irritation than the steady flow, apparently does not favour trans-intestinal contamination; consequently inclusion of a broad-spectrum antibiotic in the fluid is generally adequate in prevention of peritonitis. Another advantage of the intermittent technique is the fact that it does not predispose to 'channelling' of flow so that the dialysing surface is not reduced as may be the case with the older continuous flow method. Often a mild hypertension is observed during dialysis, but this is temporary and not a serious complication. (Interestingly enough, a similar transient hypertension is frequently seen during dialysis with the artificial kidney.) Occasionally, the presence of extensive intra-abdominal adhesions may prevent successful dialysis, by bending intestine or omentum to the abdominal wall (with risk of perforation on insertion) or by forming loculations within the peritoneal cavity (limiting the amount of fluid which can be instilled.) Infection of the peritoneal cavity is an absolute contra-indication to peritoneal dialysis and recent or extensive abdominal surgery is a relative contra-indication.

When applied to cases of acute renal failure the elevated BUN, NPN and creatinine do not respond quickly but the electrolyte, water and acid-base disturbances do. Clinical improvement is the general rule. The rapidity of response depends on the frequency of dialysis. Especially gratifying is the response in potassium intoxication, one of the most important factors in acute renal failure. In uremia, dialysis produces a good initial response, chemical and clinical, but this lasts only for a relatively short time.

The addition of dextrose to the fluid, making it up to the desired tonicity, allows dehydration of severe refractory oedematous states. It has application to conditions other than those primarily renal such as a case of congestive heart failure with oedema and ascites refractory to all conservative management in which a negative water-balance of 6.5 litres in eight hours was induced by dialysis with a solution containing 10% dextrose.

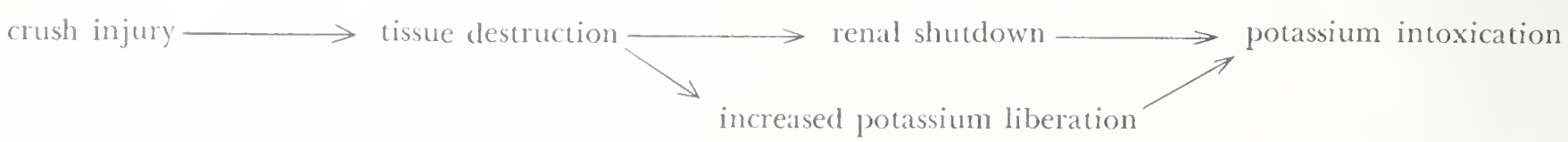
Theoretically, the procedure may be valuable in any electrolyte, water or acid-base disturbance. It has been applied with some success to hypercalcemia, and even to diabetic acidosis. Hepatic coma has been observed to respond to dialysis. This might indicate that the origin of the state is at least in part a blood-borne toxic substance. While many exogenous poisons (notably barbiturates and salicylates) have been successfully dialysed in poisoned human patients, it is probable that the urgency of the condition here weighs against the slower peritoneal method and indicates the use of the artificial kidney. However, the ready availability and ease of administration of the former is again a potent factor in its favour.

In summary, it may be stated that intermittent peritoneal lavage is a safe and effective method of artificial dialysis whose speed of action is not equal to that of the artificial kidney but which possesses the advantages of being relatively simple to apply and is not so trying a procedure for the patient.

Ion Exchange Resins

The problem of potassium retention and intoxication in renal failure is a well recognized one, and death from the various myocardial effects of hyperkalemia is a frequent termination of the state. It has been surmised that the problem is not simply one of elevated serum potassium but rather of a decreased ratio of intracellular to extracellular potassium. However, in essence the problem is one of how to remove excess potassium from the extracellular fluid compartment of an organism whose normal excretory function is deranged and whose primary pathology is often contributing to an excess liberation of potassium from the intracellular compartment to the extracellular.

Eg.:



The solution of the problem may be sought in two ways: the promotion of protein anabolism and minimization of catabolism in an attempt to retard or reverse the intracellular to extracellular transfer of potassium, and the removal of potassium from the extracellular fluid. Of the methods employed to effect the latter, the use of cation exchange resins is one of the newer and more interesting. These resins are cross-linked polymers containing acid groups (either sulphonic or carboxylic) which can exchange the H + ion for other cations in the solution in which the resin is placed.

The resin is put (per os or by enema) into the intestinal tract and is passed, having exchanged the bound cations for those in the intestinal secretions it contacts. The efficiency of the resin in removing various ions is determined by the valence of the particular ion, by the concentrations of the ions relative to the initial degree of saturation of the resin with them, and by their concentrations in the solution relative to each other. Thus, to a degree, the type and amount of ionized material bound to the resin after equilibration may be controlled by the preliminary 'loading' of the resin. As an example, for K removal from the gastrointestinal tract the resin is loaded with Na, NH, or H. In the gastrointestinal tract secretions the principal ionic components are Na and K. It has been found that the *in vivo* efficienciey of K binding is at least 50% greater than that of Na binding even with appreciable Na intake (and secretion). This natural tendency to remove K is therapeutically opportune in renal failure. It is suggested that the preferential binding may be explained on the grounds that there is active transport of Na across the colonic mucosa in excess of that of K. The mucosa competes with the resin for available intraluminal Na thus favouring the binding of K over Na.

In treatment of hyperkalemia, it has been found that preliminary loading with sodium (that is using an exchange resin 'in the sodium cycle') is the most satisfactory choice. The available alternative resins are those in the NH and H cycles but the use (and consequent absorption) of either of these cations leads to a marked metabolic acidosis, aggravating the pre-existing imbalance, and predisposing to an elevated serum K. Also, sodium is extracted with the K and produces hyponatremia (which potentiates K toxicity) and serum hypotonicity (which aggravates uremic symptoms). On the other hand, the use of a resin in the Na cycle may cause hypernatremia and overhydration with pulmonary edema and death unless strict water restriction is observed (previous day's urine output plus insensible water losses). This measure may produce a startling rise in serum Na, but without a coincident expansion of the extra cellular fluid compartment no adverse effects have been observed. Another advantage of the sodium cycle resins is the absence of mouth ulceration occasionally observed with resins of the NH or H cycles.

Cation exchange resins were introduced in the treatment of K retention in uremia by Elkinton in 1948, but the method had many pitfalls at that time the chief of which was the tendency to faecal impaction by the swollen, hydrated resin. This tendency has been reduced by using smaller mesh resins (with more cross-linkages in the polymer, making a finer molecular latticework) that do not swell to the same degree on hydration. These finer mesh resins are also more palatable to the patient. This is important since the uremic patient tends to be anorexic. Recently, the tendency toward impaction has been combatted by the combination of the resin with a potent osmotic cathartic.

The preferred route of administration is per os, since this generally produces more efficient K removal, but unfortunately most uremic patients tend to nausea and vomiting and may not tolerate the oral route. Alternatively, the resin may be instilled directly into the stomach by a nasogastric tube but here again vomiting may supervene. Also, the tube produces unpleasant irritation and the intestinal hypomotility common in uremia may render the resin useless. The instillation of the resin by enema is more often done and here the K extraction although not so gratifying as by the longer route, is still substantial.

For oral administration, resin dosage may be calculated as follows:

Normal K production 40 mEq/day (which may be reduced to 20 mEq by 100G CHO intake).

Theoretical cation binding capacity of resin x mEq/G.

Actual K binding capacity of resin x /3″/G (since Ca, Mg, and other cations are also bound utilizing 2/3 of the cation binding capacity).

Therefore, 60G/day required to reduce K stores and
20G/day required for maintenance with electrolyte-free intake.

For the rectal route of administration, lower doses are usual, since the procedure is unpleasant and debilitating. The required dose of resin is suspended in approximately 200 ml water.

When faecal impaction presents a problem the use of cathartics and enemas is helpful. One measure which deserves special mention is the administration of sorbitol, a polyalcohol of sorbose, which is poorly absorbed, non-toxic, and a potent osmotic cathartic. A dose of sorbitol sufficient to produce one or two diarrhoeal stools a day was found to be a valuable adjunct to resin therapy, preventing impaction and potentiating K removal. In fact, the sorbitol alone was found to be more effective than the resin combined with the alcohol in the actual lowering of serum K values but sorbitol is not so helpful to the actual clinical state since there is a concomitant decrease in the already depressed CO_2CP along with the diarrhoea produced.

In general, the exchange resins are safe and effective in the treatment of K intoxication in renal failure but their action is slow compared with dialysis procedures. There are cases, especially with massive tissue destruction (overwhelming infection, burns, trauma), where the rising serum K is refractory to the resin and dialysis must be utilized. However, it is felt that *prophylactically* the ion-exchange resin is extremely valuable and requires none of the trained staff and expensive equipment required for the performance of dialysis. In one study, where thirty-two patients with renal failure were treated with exchange resins as soon as the serum K exceeded 5.0 mEq/L or was noted to be progressively rising at any level, only two cases were refractory to treatment utilizing the exchange resin combined with standard measures (sodium bicarbonate infusion, glucose and insulin administration).

The resin has the added advantage of feasibility for long-term therapy which is out of the question with the artificial kidney and decidedly time-consuming and unpleasant with peritoneal lavage.

Due to lack of space the bibliography has been omitted but is available on request.

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Recent Advances

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Ed.

CONTRIBUTORS: Dr. T. S. Leeson
Dr. W. J. R. Taylor
Dr. J. W. Steiner
Dr. S. H. Bensley

Formation Of Cilia

For many years, centrioles have been thought to be involved in the formation of cilia. With the advent of the electron microscope, there has been found to be a marked similarity in structure of cilia, flagellae (animal and bacterial and centrioles).

Studies of developing rabbit trachea would indicate that cilia are formed from centrioles and microvilli — the characteristic 9 peripheral and 2 central filaments developing from the centriole, and the microvillus contributing the cell membrane to cover these filaments. As each ciliated cell in the trachea contains approximately 270 cilia, such a process must involve multiple divisions of centrioles, and, at present, there is no evidence indicating how this occurs. Presumably the entire process also continues after birth in the regeneration of ciliated cells.

A New Concept In Diuretic Therapy

The clinical introduction of the aldosterone antagonist, spironolactone, marks an important advance in diuretic therapy. The diuretic effect of spironolactone is achieved through a mechanism that differs fundamentally from that of the conventional diuretics such as the organic mercurials, the carbonic anhydrase inhibitors or the thiazide derivatives.

Spironolactone specifically blocks the effect on the kidneys of mineralocorticoids such as aldosterone. It competitively inhibits the sodium-retaining and potassium-excreting powers of aldosterone. However, it is totally inactive as a "sodium-excreting" substance in the absence of mineralocorticoids. Adrenalectomized rats, not receiving aldosterone or other mineralocorticoid, cannot be made to diurese with spironolactone. Administration of this aldosterone antagonist has been shown to be equally ineffective in patients suffering with severe Addison's disease. On the other hand, extremely large doses of spironolactone will cause moderate sodium retention, indicating that it must itself act on the kidney as a weak mineralocorticoid (an activity which is too weak to be detected at more moderate dosages). However, when given in the presence of its more potent analogue, aldosterone, it prevents the more marked sodium-retaining and potassium-excreting action by competitively binding receptor sites in the distal tubules of the kidney.

Spironolactone may prove to be the "perfect" diuretic agent. It is relatively non-toxic and by virtue of its mechanism of action does not cause potassium loss. Most patients with edema associated with congestive failure, cirrhosis, or nephrotic syndrone, show an increased production of aldosterone. The mechanisms leading to this excessive production are not fully understood but an important factor appears to be the decrease in "effective" arterial blood volume (the volume of blood between the heart and peripheral tissues) that is associated with these conditions. However, the increase in sodium and water reabsorption caused by the excess aldosterone that is produced does not correct but instead aggravates the basic defect and aldosterone production continues at a high level. Spironolactone has been shown experimentally and clinically to effectively interrupt this vicious circle. Its single undesirable characteristic is its high cost (about one dollar per 100 mgm. tablet or four dollars for a 400 mgm daily dose).

Mechanism Of Injury In Serum Sickness

Until recently, the pathogenesis of serum sickness was known to be the result of antigen-antibody interaction, though the exact conditions under which this occurred were not known.

The theory suggested one of two possibilities:—

(1) — *antigen* attached to cells, and circulating antibody reacted with it.

or — (2) — that *antibody* attached to cells, and circulating antigen reacted with it.

It has now been demonstrated that complexes of antigen and antibody formed *in vitro,* in the

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In each of these spastic conditions, the usefulness of BUSCOPAN is enhanced by its virtual freedom from such commonly encountered side effects as sedation, dryness of the mouth, and visual disturbance.[1,2,4-7]

Recommended dosage: 10 to 20 mg. (1 to 2 tablets) has been found to be the average single effective dose; however, dosage may be increased in acute conditions where pain is severe. A dose of 10 mg. three to five times a day is recommended for prolonged conditions such as peptic ulcer. *Supplied:* BUSCOPAN Tablets, 10 mg.—bottles of 100.

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presence of antigen excess, are capable of producing the lesions of serum sickness when given intravenously to mice.

Thus it appears that such immune complexes are toxic to cells, *per se,* without necessarily having to attach themselves to cells.

This mechanism may be operative in all immediate (Arthus) type immune reactions.

R. T. McCLUSKY & BENACERROF B.
Asm. J. Path. 1959, 35:275

High Polymer Chemistry — Applications To Biology

The science of high polymer chemistry has developed in recent years with the synthesis of plastics, resins, and fibres for industrial and commercial use. The study of the physical properties of these synthetic polymers has shed light on the physical properties of biological ones; and application of studies of their chemistry is one of the newer approaches to connective tissue histology.

In the body, high polymer chemistry is used both within and without the cell — within, in the formation of *chromosomes, cell walls* and *cytoplasmic* fibrils; and without, in *intercellular substances,* forming the internal environment of practically all cells of the body.

Physical Properties

The studies of physical properties of synthetic polymers have many applications in biological research.

Studies of water-binding capacity of certain polymers give insight into the mechanism of body water distribution.

Ion exchange resins provide a new concept of *ion transfer* and mineral absorption in intercellular substances.

Resilience, rigidity, and tensile strength of synthetic polymers provide a means of interpreting supportive and barrier functions in their biological counterparts.

Chemistry

Four main types of polymers occur in connective tissue intercellular substances — (1) polysaccharides (2) polypeptides (3) polyelectrolytes (4) combinations.

Antihistaminic Drugs In The Treatment Of The Common Cold

Antihistaminic drugs as a group are pharacological substances which resemble histamine in chemical structure and specifically antagonize the biological activity of this compound as a result of the similarity. The most frequent use of the antihistaminic agents is in the treatment of seasonal hay fever and the common cold.

Antihistamines are very effective in seasonal hay fever or any condition where there is an allergic component with histamine release. Full or partial relief will usually be provided in over 80% of patients so selected. However, the signs and symptoms of the common cold in non-allergic individuals are not appreciably influenced.

A number of clinical reports have appeared in the literature extolling the virtues of the antihistaminics both as prophylactic agents against the common cold and as agents which "abort" the disease when taken during its early stages. The most notable of these is the work of Brewster[1] in 1950. However, other studies [2],[3] have indicated that when subjects, free of any personal or family history of allergic disorders, are given by double blind technique, either an antihistaminic agent or a placebo, approximately 50% of each group will experience subjective improvement. Feinberg[4] concluded that the only action of antihistamines in the common cold is to reduce nasopharyngeal secretions and perhaps the tendency to sneeze but only at the expense of some sedation and decrease in cerebral efficiency. Considering the untoward reactions, antihistamines are not indicated in the treatment of the common cold where there is no allergic component.

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Acute Renal Failure

by James Paupst, B.A.

Diagnosis

Acute renal failure may be the complication of many medical, surgical, and obstetric situations. To include all the causes of acute parenchymal injury to the kidney under the term, "acute renal failure", may be misleading clinically. The term should be confined to such clinical entities as shock kidney, crush syndrome, traumatic uremia, burn nephritis, haemoglobinuric nephrosis and toxic nephrosis. (30) This separation of causes is an important concept because of differences in treatment and prognosis.

A knowledge of the differential diagnosis of acute urinary suppression requires suspicion of its development. When a patient, for example, suffers a crushing injury to the skeletal muscles, the anticipation of the development of acute renal failure is a key thought in the approach to the situation.

The core of this article is the recognition that *early diagnosis is difficult, and yet essential.* Therapy begun to prevent its development may be dangerous when it has appeared. The consideration of criteria available for early diagnosis leads to the conclusion that no one criterion is absolutely suitable:
diminished urine volume has not been found a suitable diagnostic criterion. Indeed, oliguria can occur with normal renal function. Water restriction in a normal subject will produce urine volumes of approximately 400 ml. per twenty-four hours, with a specific gravity of 1.030, or higher, and osmolarities of greater than 1200 milliosmols per litre. (31)

If salt and protein are omitted from the diet, however, as may occur before and after operation and during prolonged parenteral fluid therapy, obligatory solute excretion can reach levels as low as 300 milliosmols per litre. (32)

This osmolar load can be excreted in a urine volume of 300 to 500 mls. With a specific gravity of 1.008 to 1.014, or even smaller volumes if water is also restricted. Thus, one can have *physiologic oliguria* with either high or low urine concentrations as a result of variations in water and solute intake. In contrast, acute renal failure has been associated with minimal oliguria, normal urine volume or even polyuria. (33-35)

Franklin and Merrill underline the observation that elevated B.U.N. levels may be confusing since protein catabolic response to surgery, trauma, burns, transfusion reactions and gastrointestinal or internal bleeding occur with or without the subsequent development of renal failure. Obversely B.U.N. may rise only 10-15 mg. per 100ml. daily in anuria without excessive trauma, fever or infection. *Therefore, early diagnosis of renal failure must frequently be made on the basis of other criteria than urine volume or blood urea nitrogen levels.* (36)

The composition of urine provides information useful in diagnosis. In various states of acute circulatory insufficiency that precede the development of renal failure, renal ischemia develops and may be associated with small urine volume, with initially high specific gravty. Sodium reabsorption is almost complete; urea is the chief solute. However there is a characteristic alteration with the development of acute tubular neorosis. Urinary urea decreases markedly to ratios of urinary to plasma urea of five or less and sodium appears in the urine in abundant concentrations (40-90 M Eq per litre) . (37)

However, Sevitt and Graber noted a low urinary sodium value in the majority of burned patients with renal failure. *Low urea and high sodium concentrations in the urine suggest acute parenchymal renal failure.*

Pathogenesis

As a response to depletion of the renal circulatory load, vasoconstriction occurs with diminished excretion of sodium and water. This depletion in volume is associated with increased secretion of aldosterone and antidiuretic hormone. And as long as these vasoconstrictor stimuli are of short duration, they play a chief role in maintaining homeostasis. However, when these stimuli are pronounced and acute, oliguria and low urinary sodium concentration may arise. This situation is initially reversible, but may proceed to ischemic changes with or without anuria. Sheehan and Moore suggest that cortical necrosis is a manifestation of a more prolonged, severe renal ischemia rather than an entity etiologically different from tubular necrosis.

The rate of urine flow, or concentration of the urine as well as renal ischemia is important in the pathogenesis of renal failure. This in turn suggests that pigment excretion (this occurs in the liberation of blood and muscle pigments after trauma, burns, and transfusion reactions or in paroxysmal hemoglobinurias, or myoglobinurias) in the presence of minimal urine flows may result in a gel that occludes the tubule or, less probably has a toxic action on the tubular cells. (38)

Clinical Setting (39)

1. Intravascular reactions
   a) Incompatible blood
   b) Intravascular haemolysis from distilled water in transurethral prostatectomy.
   c) Other acute haemolytic anurias
2. Traumatic shock
   a) Operative shock
   b) Crush syndrome
   c) Multiple fractures
   d) Severe burns
3. Haemorrhagic Shock
   a) Uteroplacental damage
      1. Haemorrhage at time of delivery
      2. Abortions
   b) Other acute haemorrhages.
4. Medical shock
   a) Acute fluid and electrolyte loss
   b) Acute pyogenic infections
   c) Acute haemorrhagic pancreatitis
   d) Diabetic coma
5. CCl_4 poisoning
6. Sulphonamide intoxication

Pathophysiology

The multiplicity of causes resulting in the genesis of acute renal failure, converge ultimately on the pattern of anuria, a subsequent diuretic period and recovery of function. A nephrotoxin produces an uniform cellular necrosis in a large segment of the proximal tubule down to, but not including the basement membrane. The association of ischemia produces complete destruction of any part of tubular continuity including the basement membrane.

The explanation however of anuria and subsequent diuresis has not been resolved.

The explanation however of anuria is due to decreased renal blood flow. Some explain anuria as a result of increased interstitial pressure secondary to renal oedema.

The onset of diuresis is marked by a daily increase of 50 to 100 per cent in urine volume over each preceding day. (40)

It should be noted that urea clearance does not keep pace with endogenous urea production so that blood urea may rise, or remain at a higher plane for several days after the onset of the diuretic period. Franklin and Merrill remark on the rapidity with which tubular function returns: sodium can be efficiently reabsorbed to 10-20 milliequiv. per litre of urine by the seventh to tenth day of diuresis. Obviously then *the state of hydration at the onset of diuresis will be the most important determinant of how much sodium, potassium and water must be replaced.*

Clinical Course and Treatment

Body Composition

There is a rapid catabolism of fat and protein during oliguria. Proper fluid therapy can be gauged from daily weight loss, which varies from 0.2 to 0.5 kg. in the average anuric patient. (41), (42) Preventing or minimizing this loss increases the tendency to overhydrate. In the average case of acute renal failure a daily fluid intake of 400 ml with replacement of renal and gastrointestinal losses is sufficient to keep water balance. (43)

Franklin and Merrill comment that hyponatremia and hypochloremia have long been regarded as characteristic features of the anuric period, and that hyponatremia can be prevented however by the maintenance of accurate water balance.

Potassium is released from depleted glycogen stores, destroyed red blood cells, burning of protein and fat stores, and the extracellular shift out of cells effected by metabolic acidosis. The rise in serum potassium characterizes lengthy anuric states. A palatable sodium cycle resin (Kayexalate) has been found effective in the prevention and treatment of potassium intoxication. It is used in conjunction with sorbitol to produce gastrointestinal emptying. (44)

Caloric response.

The use of 100Gm. of carbohydrate daily is still recommended for preventing ketosis and minimizing protein breakdown. In the presence of coexisting trauma, tissue necrosis or infection, larger amounts than 100 Gm. minimally affect protein catabolism.

Nutrition, when possible, should be effected orally. This augments salivary flow, and fissuring of the pharynx is avoided. Hard candy is a good source of pure carbohydrate. Parenteral administration of concentrated dextrose solutions are given intracaually.

Clinical Course

Oliguria is usually manifested within 24 hours of the precipitating episode. The time of onset is difficult to ascertain when the cause is infection, or severe fluid or electrolyte loss. Complete absence of urine should cause one to suspect mechanical block. The oliguric urine usually has a specific gravity near 1.010 and is nearly neutral in reaction. (Recall the previous discussion about variable patterns in S.G. urinary volume, and B.U.N.) Diuresis begins usually in 5-15 days, the average being 9 days. The output rises from 1500-2000 cc up to 4,000 or 5,000 cc.

Complications

Infection

During the last several years infection has become a most important cause of anuric death. And in one series (Parsons and McCracken) it was the chief cause. Sepsis may be overlooked because of confusion with uremic symptoms. One should be aware of the delay in the appearance of granulation tissue. And when an antibiotic is selected, if it is excreted renally, the dosage should be reduced.

Gastrointestinal

Nausea, vomiting diarrhoea and occasionally ileus result from acute renal failure. The altered gastric motility may be related to the abnormal chemical environment.

Cardiac

Arrhythmias, most commonly atrial fibrillation and supraventricular tachycardia and ventricular tachycardia are associated with the rise of serum sodium, and decrease in serum potassium.

Hoemostasis

Bleeding occurs more commonly in acute than chronic renal failure. Recently both qualitative and quantitive platelet defects have been found in acute renal failure. (45)

In those anuric patients in whom bleeding contributed to death, thrombocytopenia was found. And the use of fresh platelets or plasma may be of value in the treatment of severe uremic hemorrhage.

Acknowledgment: The author wishes to acknowledge the assistance of Dr. Nicholson of the Department of Pathological Chemistry.

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ABSTRACT: *Auscultation of the Skull in the Detection of Osteolytic Lesions.* D. Green and R. J. Joynt: New England Journal of Medicine, 264:1203, 1961.

The authors describe a case of metastatic carcinoma of the parietal bone in which a difference was noted on auscultation of vocal resonance over normal and abnormal skull bones. Using the diaphragm of the stethoscope and the test phrase *ninety-nine* it was noted that the voice was clearer and higher pitched over the metastases. Phonocardiographically it was also demonstrated that transmission of more complex wave forms occured through the lesion. It was suggested that this is due to decreased filtering by the abnormal bone and that auscultation may be of practical clinical significance in the detection of osteolytic lesions.

A. F. D. C.

Interesting Cases

Case No. 1

M.L.

This thirty-five year old woman, married for eight years but with no children, came to the Medical Clinic of the Toronto General Hospital in June, 1961, complaining of weakness of both feet for two years.

As long as she can remember, she had weakness of both forearms and hands, difficulty in lifting her head up from a pillow, and difficulty in lifting herself to a sitting position without the aid of her hands. She had difficulty in walking manisfested in a "waddling" gait and dragging of her feet. Due to her weakness, she walked flatfooted with all her weight on her heels. Her weakness was worse after eating and was not affected by atmospheric temperature. Her left eye was operated at the age of 17 for muscular imbalance. There has been no change in voice, vision, and ability to chew or swallow, but she has had drooping of her eyelids for a long time. She has had no weight loss and does not report having had temperature intolerance. Her menstrual periods are regular, the onset having been at age fifteen.

The patient's father had a cataract removed at the age of 60, and her mother has lateral strabismus of the left eye. One brother, aged 26, has weak arms, ptosis of his eyelids, a drooping mouth, and is becoming bald.

Physical examination revealed a thin middle-aged woman of thirty-five years whose face was remarkably expressionless. Close scrutiny of her hair showed slight temporal alopecia. She had moderate bilateral ptosis but showed no extraocular weakness. The periorbital and facial muscles were weak. This became evident when she showed difficulty in smiling and a lack of facial expression. Her speech was slightly slurred. There was marked weakness and atrophy of the sternomastoids. The tongue was small, and myotonic on percussion.

Examination of the motor division of the nervous system revealed moderate bilateral weakness of the shoulder and pelvic girdles and of the abdominal muscles. There was moderate weakness and wasting of the muscles in the forearms and hands, legs and feet. It was noted that there was no weakness of the biceps, triceps, quadriceps or hamstrings. All tendon reflexes were absent.

When the patient was asked to grasp the examiner's hand, she found it difficult to relax her grip but her performance improved with subsequent trials. When the thenar muscles were percussed with the reflex hammer, there was prolongation of the contracted phase.

These observations led to a diagnosis of myotonic dystrophy. Synonyms for the condition are myotonia atrophica or myotonia dystrophia.

The patient was treated with five grains of Quinine four times each day. On a return visit one month later she stated that the Quinine improved the use of her hands and that she was able to walk faster. However, she complained of a new symptom, ringing in the ears. Tinnitus is an undesirable side effect of Quinine. The dose in her case was reduced to five grains two or three times daily.

P. A. Korhonen 6T2

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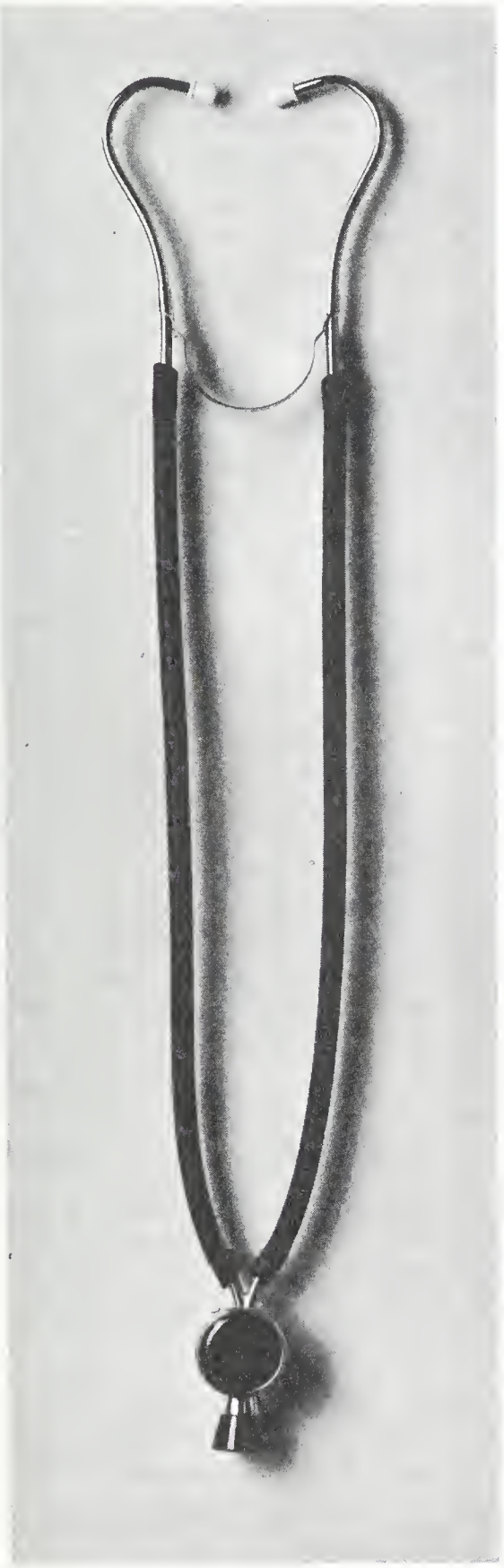

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Summary of Renal Physiology
(after Samson Wright 1961)

	Glomerulus filtered/24 hr	Proximal convoluted tubule	Distal convoluted tubule, loop of Henle and collecting tubules	Urine excreted /24 hr
WATER	170-180 l.	7/8 reabsorbed passively secondary to sodium	*Loop of Henle* impermeable to water; *collecting tub.* facultative reabsorption controlled by ADH	1.5 L
TONICITY of fluid	Isotonic	Isotonic	Hypotonic or isotonic	hypertonic up to 5X O.P. of plasma
SODIUM	560g. (24000 meq)	7/8 reabsorbed actively in exchange for H^+ (Obligatory reabsorption)	active reabsorption in ascending loop of Henle and dist. con. tub. under control of aldosterone (facultative reabsorption)	5 g. (210 meq)
POTASSIUM	29 g. (740 meq)	completely reabsorbed	secreted in competition with H^+ in Na^+ exchange	2.2 g. (56 meq)
HYDRONIUM (H^+)		excreted in exchange for Na^+, isohydric with HCO_3 reabsorption, thus no pH change	"pari pasu" transfer in Na^+ exhange and exceeds available HCO_3 then $H^+ + HPO_4 \rightarrow H_2PO_4$ buffer system to acidify urine	pH 6.0-6.5 normally
NH_3			stimulated by potential metabolic acidosis, amino acids (60% glutamic) by glutaminase $\rightarrow NH_3$ within tubule cell; below pH 6.0, NH_3 diffuses into tubule $NH_3+H^+ \rightarrow NH_4$ and conserves Na^+	
CHLORIDE	620 g. (18700 meq)	4/5 passively reabsorbed secondary to Na^+	reabsorbed secondary to Na	9 g. (257 meq)
BICARBONATE	255 g. (4180 meq)	majority reacts with H^+ (from solium exchange) $\rightarrow H_2CO_3 \rightarrow H_2O + CO_2$; CO_2 diffuses into tubule cell $CO_2 + H_2O$ (carbonic anhydrase) $\rightarrow H_2CO_3 \rightarrow H^+ + HCO_3$; HCO_3 returns to plasma and H^+ generated for Na^+ exchange	remained reabsorbed in a similar mechanism in dist. con. tub.	0.1 g. (1.6 meq)
PHOSPHATE	5.1 g (170 meq)	130 meq reabsorbed $HPO_4/H_2PO_4 = 4/1$	acts as a buffer to accept H^+	1.2 g. (40 meq)
GLUCOSE	170 g.	all reabsorbed		none
UREA	51 g.	21 g. reabsorbed		30 g.

TABLE 1.

Recent Developments in Diuretic Agents

R. O. Davies Ph.D., 6T2

When one attempts to outline the material which might be discussed in the field of Renal Pharmacology a number of topics immediately present themselves, no one of which concerns only the kidney. Three problems in renal therapeutics for which drugs are useful include antibiotics for pyelonephritis, antihypertensive drugs for glomerulonephritis, pyelonephritis and nephrosclerosis, and diuretic agents for problems in fluid retention. Each of these fields has advanced both recently and rapidly. The last field has been selected because of the recent achievements in oral therapy following the introduction of chlorthiazide and its analogues, and because of the increased understanding of renal physiology and pharmacology using new investigative techniques such as "stop-flow" analyses and accurate electrolyte determinations.

In this rapidly expanding field, it has been possible to recount material only from review articles rather than from the original literature. This writer has attempted to summarize the present state of knowledge in a form useful to medical students. Renal physiology as outlined in Samson Wright's "Applied Physiology", 1961, has been summarized in Table I; a list of currently used diuretic agents with their trade names and dosage will be found in Table II.

Mechanisms of Various Types of Oedema

Cardiac oedema is due principally to inadequate cardiac output and this in turn reduces renal blood flow, perhaps to as much as half of normal; this causes a decrease in glomerular filtration. While this affects sodium excretion, influences on tubular reabsorption of sodium appear more important. Secondly aldosterone is believed to be involved because of the increased quantities excreted in the urine of patients suffering from cardiac oedema.

Hepatic disease, primarily cirrhosis, produces oedema and later ascites. Oedema is at first due to hypoproteinemia secondary to decreased plasma protein formation; ascites develops when portal hypertension is added to this deficiency. When sufficient fluid has been sequestered in the abdomen, and other tissues, to decrease circulation blood volume a stimulus to secrete increased quantities of aldosterone is added to the decreased ability to metabolize this hormone.

Nephrotic oedema is characterized by increased permeability of the glomerular membrane to protein; this loss induces hypoproteinemia and marked proteinuria. A decreased glomerular filtration rate reduces sodium excretion, and a decreased circulation blood volume stimulates aldosterone release to increase sodium reabsorption; the effect is sodium accumulation. Also, increased protein catabolism releases potassium, and this ion may be lost to the body when diuresis begins.

Other oedemas include premenstrual oedema which may be secondary to increased oestrogen and/or progesterone, to increased aldosterone and perhaps to antidiuretic hormone. Eclampsia causes increased sodium reabsorption but this may not be due to increased aldosterone secretion. The oedemas of Kwashiorkor and starvation may be traced to hypoproteinemia, and differ from that found in nephrotic syndrome only in that there is no renal damage.

In short, a common finding is accumulation of sodium in the body, and secondarily other ions. The body then holds water in increased quantities. The primary mechanisms which in turn are responsible for this state include decreased cardiac output, decreased plasma proteins, and increased aldosterone levels. Treatment can be directed to decreased intake of and increased removal of sodium as well as to modifying the underlying mechanism influencing sodium accumulation.

Diuretic Agents

Definition. Those substances which increase the loss of water and ions from the body by an action primarily on the kidney.

Classification. Though any such scheme is somewhat arbitrary, this may be established on the proposed mechanism of action. It does not always eliminate overlap.

I. Primary reduction of sodium ion reabsorption.
   a) xanthines and aminouracils derivatives
   b) mercurial diuretics
   c) inhibitors of carbonic anhydrase

d) thiazines and benzothiadiazines derivatives
e) aldosterone antagonists
f) potassium salts

II. Secondary reduction of sodium reabsorption.
a) osmotic diuretics (urea, sucrose, mannitol, etc.)
b) inhibitors of aldosterone secretion (Amphenone B)

III. Increased sodium filtration.
a) acidifying salts (Ammonium chloride)
b) Corticosteroids (these also increase tubular reabsorption)
c) plasma expanders.

Discussion of these substances will be limited to those agents more commonly used in therapy, with emphasis on those of more recent origin. No discussion of the corticosteroids used in treatment of the nephrotic syndrome of children has been included. This classification fails to include inhibitors of antidiuretic hormone (ADH); only two examples of which are commonly recognized, water and ethanol, and neither of which are practical therapeutically.

Xanthine and Aminouracil Derivatives.

This group of drugs, produced by selective methylation of the pyrimidine nucleus, includes caffeine, theophylline and theobromine, and these have potential actions on kidney, brain, heart and muscle. The more important actions of theophylline are an increase in cardiac output and a decrease in tubular reabsorption of sodium. Potassium excretion occurs on a secondary basis. In practice, conjugation with an organic base such as ethylenediamine (aminophylline is theophylline with ethylenediamine) increases solubility and facilitates absorption. Tolerance to the diuretic effects are reported after repeated administration.

Two compounds which are related to aminouracil, namely aminometradine (Mictine) and aminometradine (Rollicton) were introduced as diuretic substances which appeared to be better tolerated. However, side effects include nausea, vomiting and diarrhoea in addition to the development of tolerance to the diuretic activity.

Mercurial Diuretics.

Mercury has been known as a duretic substance for centuries. The introduction of organic mercurial agents in 1920 marked a significant advance in the therapy of oedema. Mercury, in this form, while less active is substantially less toxic and produces less irritation upon injection.

Chemically these agents are derivatives of mercuripropanol [R-CH_2-C[O-Y]H-CH_2-HgX]. Substitution at "R" constitutes the major variation; at "X" conjugation with organic bases such as theophylline or mercaptoacetic acid serves to greatly increase the rate of absorption after injection and to decrease toxicity. Mercaptomerin (Thiomerin) introduced in 1949 can be given by subcutaneous injection and has little cardiac toxicity (ventricular fibrillation has been reported after intravenous administration of mercurial diuretics). These agents, when given orally are poorly absorbed and cause nausea and vomiting, abdominal pain and diarrhoea; chlormerodrin has been introduced as an oral agent which may be better tolerated than other mercurial compounds. However, in view of the dose of mercury necessary for activity together with only moderate potency and since the introduction of chlorthiazide such oral mercurial therapy offers no advantage.

Govaerts and Bartram established that the diuretic effects of mercurial agents was renal, that mercury was fixed to renal cortex and that high doses could cause renal damage. This activity is primarily a depression of sodium ion reabsorption in the proximal convoluted tubule; glucose reabsorption and secretion of weak acids at this site are also depressed. While it is recognized that chloride is lost in greater quantities than sodium, this can be accounted for by decreased depression of the sodium shunt in the distal convoluted tubule; this allows some sodium exchange for H+ or potassium while the chloride anion escapes. Biochemically, mercurial compounds which are active as diuretic substances have been shown to inhibit –SH enzymes *in vitro,* and to deplete protein bound–SH groups in the proximal convoluted tubules *in vivo.* Both this biochemical activity and diuretic activity can be reversed by dimercaptol (BAL). However, the relationship between –SH enzymes and the ion carrier system or its energy supply has yet to be demonstrated.

Overactive treatment with mercurial diuretics can produce metabolic alkalosis, and under these circumstances the patient becomes refactory to therapy. This may be attributed to excessive loss of chloride over sodium, and replacement by bicarbonate (bicarbonate reabsorption in the renal tubules has not been affected). Administration of ammonium chloride or lysine chloride can

restore extracellular chloride and reestablish diuretic activity.

Inhibitors of Carbonic Anhydrase

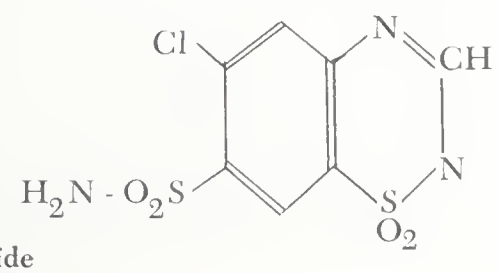
Carbonic anhydrase is an enzyme which is found in kidney, blood, brain and in the eye, and has been shown to accelerate the reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$. Sulphanilamide and its derivatives have been shown to inhibit this enzyme, and some are effective as diuretics, or as anticonvulsants as well as being useful in the treatment of glaucoma.

Acetazolamide (Diamox), an inhibitor of carbonic anhydrase, blocks the removal of H_2CO_3 and as a result bicarbonate accumulates. Excretion of this bicarbonate due to decreased absorption in the renal tubules, increases urine volume and can produce a metabolic acidosis with an alkaline urine. Decreased excretion of H+ allows potassium to escape via the sodium exchange mechanism; the alkaline urine tends to impede ammonium diffusion. Refactoriness develops in the face of decreased plasma bicarbonate but is not restored by replacement of this ion; other factors, as yet unclear, appear to be involved.

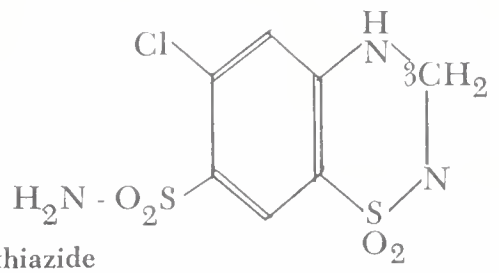
As a therapeutic agent, acetazolamide has a rapid and shortlived effect; a single dose reaches a peak effect in two hours and has completely disappeared within sixteen hours. However, this agent when used alone is not sufficiently potent to be effective in other than mild oedematous states.

Thiazine and Benzothiadiazine Derivatives.

The introduction of chlorothiazide in 1957 by Beyer and associates at Merck and Company, Inc., marked a significant advance in the oral therapy of oedema. While the investigation, originally intended to detect carbonic anhydrase inhibiting activity of compounds related to sulphonilmiade, showed that while these compounds were weak inhibitors of this enzyme, they had high nateuretic activity which was independent of and additive to the effect of mercurial diuretics. This activity is confined to the renal tubules and is characterized by high sodium and secondary chloride excretion, some bicarbonate loss (less than acetazolamide) and significant potassium depletion.



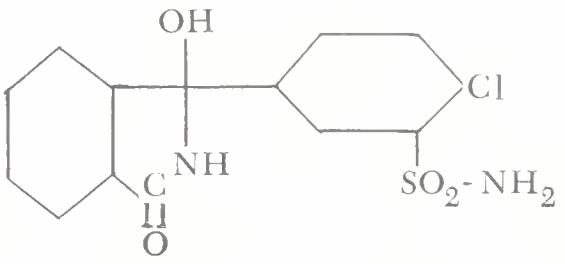
Chlorothiazide



Hydrochlorothiazide

The formula of the original compound, chlorothiazide, to be introduced for clinical use is shown above. The dihydro derivative hydrochlorothiazide, is some twenty fold more active and qualitatively similar to the parent compound except for decreased carbonic anhydrase inhibiting activity. Substitution of the chlorine atom with a trifluoromethyl group in the hydrochlorothiazide molecule decreases potency moderately and reportedly decreases potassium excretion. Benzyl substitution, dichloromethyl substitution and benzylthio methyl substitution at C_3in hydrochlorothiazide produces benzyhydroflumethiazide and trichloromethiazide and benzthiazide respectively.

Finally Hygroton was introduced as a compound with prolonged action and relatively little potassium loss.



Chlorothiazide and its congeners are orally active, as well as by parenteral routes, are well tolerated and are relatively non-toxic. They are not subjected to rapid development of refactoriness after repeated use. Reportedly the compounds are safe in the presence of preexisting renal damage; this, in the view of some workers, is a contraindication for mercurial therapy. The only caution is attention to the possibility of potassium depletion, especially in cirrhotic patients. Lastly it appears that these compounds enhance the antihypertensive activities of resperine and hydrallazine, perhaps as part of their diuretic mechanisms.

Aldosterone Antagonists

Aldosterone, the principle adrenal mineral corticoid, promotes rapid reabsorption of sodium and secretion of potassium in the distal convoluted tubule in response to decreased "effective" arterial blood volume in the region of the diencephalon

and/or the carotid sinus. This effect may be mediated by the release of glomerulotropin from the diencephalon. Aldosterone activity may be blocked both by preventing the release and/or synthesis of adrenal corticoids, as seen with Amphenone B or adrenalectomy, or by blocking aldosterone receptor sites, for example spironolactin. It has been demonstrated that spironolactone (Aldactone) can reduce that oedema dependant on elevated aldosterone levels present in the nephrotic syndrome, congestive heart failure, and cirrhosis. Oedema, in these and other conditions, is often due to more than one mechanism and this is confirmed by the apparent failure of therapy in some patients. Sodium loss and secondarily water loss, brought about by spironolactone is enhanced by a low sodium intake which apparently elevates the secretion of aldosterone. Spironolactone also reverses, in part, the secretion of potassium attributed to aldosterone, especially during low sodium intake. About 40% of patients with oedema and ascites secondary to cirrhosis respond to 200-2400 mgm. per day spironolactone with significant loss of sodium, water and weight. The administration of spironolactone to cirrhotic patients previously unresponsive to mercurial or thiazide diuretics, produces a marked diuresis in the presence of combined therapy with these agents and spironolactone. Patients with congestive heart failure respond to combined medication; cases of nephrotic syndrome which fail to respond to glucocorticosteroids, reportedly respond to spironolactone or to spironolactone plus other diuretics. Finally large doses of spironolactones are useful to reverse the metabolic abnormalities of primary aldosteronism.

Disadvantages of presently available antagonists

DIURETIC AGENTS USEFUL IN THERAPY

Generic Name	*Trade Name*	*Preparation and/or Dose*
Xanthines		
Aminophylline	Same	Tabs 100 and 200 mgm. Amps 0.5 G/10 c.c. I.V.
Amino Uracils		
Aminometradine	Mictine (Searle)	
Amino	Rollicton (Searle)	
Mercurial		
Mersalyl	Salyrgan-Theophylline (Winthrop)	0.5-1.0 cc. I.V. or I.M. (never S.C.) daily or P.R.N.
Meralluride	Mercuhydrin (Lakeside)	1-2c.c daily or P.R.N. I.V., I.M. or deep S.C.
Mercaptomerin	Thiomerin (Wyeth)	0.5-2c.c. daily or prn S.C. (I.M. or I.V.)
Chlormerodrin	Neohydrin (Lakeside)	Oral—tab. i. t.i.d.
Carbonic Anhydrase Inhibitor		
Acetazolomide	Diamox (Lederle)	250 mgm. tabs, 500mgm/cc 5mgm/Kg. once daily
Benzothiadiazines		
Chlorothiazide	Diuril (Merck)	Tablets—i or ii once or twice daily 250 and 500 mgm.
Hydro chlorothiazide	Hydrodiuril (Merck) Esidre (Ciba) Aquarius (Frost) Oretic (Abbott)	25 and 50 mgm.
Hydroflumethiazide	Saluron (Bristol)	50 mgm.
Benzydroflumethiazide	Naturetin (Squibb) Neo-naclex (Glaxo-Allenbury)	2.5 and 5 mgm.
Trichlormethiazide	Naque (Schering)	2 and 4 mgm
Benthiazide	Exna (Robbins)	50 mgm
Phthalamudine	Hygroton (Geigy)	100 mgm
Aldosterone Antagonists		
Spironolactone	Aldactone (Searle)	100 mgm dosage varies widely

TABLE 2.

include slow onset of response (maximal only after 3 days) and a similar persistance of effect, some drowsiness and ataxia. Last but not least, spironolactone costs about one dollar per 100 mgm tablet. Without doubt further advancement in this area will be useful in therapy.

Conclusions and Summary

In the last two to three years management of oedema has been facilitated by the discovery of chlorthiazide and its analogues; further advances in therapy are now developing with the use of antagonists of aldosterone. Both these two types of diuretic agents, as well as mercurial drugs, affect primarily sodium excretion but each has its own mechanism and combined therapy is useful. Chlorothiazide has two advantages and one disadvantage over mercurial agents. Firstly, the agents are as active orally as when given parenterally, and secondarily the agents much less toxic and appear to be safe in preexisting renal damage. The only major danger is potassium depletion; this can be overcome by replacement therapy. Aldosterone antagonists offer a further avenue of approach to treat patients whose oedema is resistent to other agents; results of treatment using these drugs and chlorothiazide are impressive.

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Letters to the Editor

Dear Sir,

In this morning's mail I received the April number of the Medical Journal. This is the first time that I have seen this magazine, but then I have been in retirement for many years. I don't need it any more than *a cat needs two tails,* but I shall always be interested in reading your editorial remarks, and I always like to encourage the home product.

Sincerely,

J. Gordon Gallie 1T0.

Dear Sir,

I am renewing my subscription to the University of Toronto Medical Journal not because I really need another journal to read but as a token of appreciation of the excellent job that the producers of the journal have done. It is quite the best publication of the kind that I have seen. Many of last years issues are well worth keeping on file for reference.

The second reason for continuing my support is that I am interested in anything which is likely to improve the ability of our graduates to express themselves clearly. As Chairman of the Editorial Board of the Canadian Journal of Surgery I, of course, am very aware and indeed often distressed that so many doctors write so badly. As you have suggested it extends even to inability to spell correctly. Let me assure you that the deficiencies are by no means confined to graduates of this school.

With best wishes.

Yours sincerely,

Robert M. Janes.

Dear Sir,

I appreciate the efforts which are being made in respect to the Medical Journal and I am aware of some of the difficulties which face its editorial staff, having been an Assistant Editor in the early years of its establishment. I read the articles in the Journal which are of interest to me and would be possibly prepared to accept an appointment on your newly formed consulting committee, although you should be aware that the amount of time spent on committees seems to be inversely related to the number on which the Faculty are asked to serve. I feel that the Journal was established and should be primarily an undergraduate organization and that the Faculty should interfere as little as possible with its function.

Sincerely yours,

D. E. Cannell, M.B.,

Professor and Head,
Dept. of Obstetrics and Gynaecology.

Book Review —

Relief of Symptoms — 2nd edition by Walter Modell. The C.V. Mosby Co. Publication date: June 1961. Price $11.50. 375 pages.

The author offers this book as a practical guide to the problems of providing patients with relief from distress. He expresses concern in his preface because so little of the medical literature available to-day is concerned directly with the relief of symptoms as such. His main argument throughout the book is "that what the symptom causes can be as important as what causes the symptom". With this in mind he has discussed the measures available for the relief of twenty-seven symptoms which represent at least ninety-five per cent of those which bring patients to a doctor's office.

Most of the material in the book is probably "as old as the hills" for experienced clinicians (although it is alarmingly new for some of us who are undergraduates) but the organization of the facts is truly original. The author's vast knowledge of pharmacology and therapeutics, his ability as a medical writer added to his extensive clinical experience have resulted in a book of unusual value for advanced undergraduates and recent medical graduates.

We recommend this book very highly to students in the third medical year. We suggest that a careful study of this book during the summer prior to the final medical year would result in excellent preparation for the months ahead when the care of patients will become the responsibility of the student and interne in an increasing way.

W.O.S.

Essentials of Neurology. John N. Walton, M.D., M.R.C.P. J.B. Lippincott Co., 422 pages, $6.75.

This book has been written both for the student and the general practitioner. It is not intended as a reference book with details of physiology and pathology, but it outlines the essential facts that are needed in clinical medicine. Highly specialized techniques are only mentioned because this text is not written for the specialist.

Half the book is given to symptoms and signs and investigation of neurological disease. Some of the topics discussed here are pain, disorders of speech, apraxia and agnosia, disorders of consciousness, special senses, the sensory and motor systems.

The remainder of the book deals with specific disease states under the headings: Development, Hereditary and Degenerative Disorders, Trauma, Infection and Allergy, Demyelinating Diseases, Neoplasms, Vascular Disorders, Disorders of Lower Motor Neurone and Voluntary Muscles, and Metabolic Disorders.

Finally, a very brief outline of principles of treatment is given. This section is very short, but one must remember that the writer is aiming primarily in setting forth the basic principles of neurology to which further knowledge can be added.

The book is written in clear easily understood language. It is very sparsely illustrated, but the illustrations contained are helpful.

For the student who wishes to learn more neurology than can be found in a general medicine text book, but who does not want a large amount of material to dig through, this book is an excellent investment.

M.L.W.

Aids to Histology by G. H. Bourne, D.Phil., D.Sc. Seventh Edition, 1960. Macmillan of Canada; 168 pp.; $1.80.

A member of the famous Aids series, Aids to Histology, in its 1960 edition, presents an up-to-date review of the classic facts and latest developments in this field. The book is directed to the medical student and should be regarded as a technical summary of the salient facts. It is definitely not a simplified course in histology. Although rather sketchy on some sections, it generally points out the important features of most of the tissues.

While this little handbook will never replace Ham's classical text, it could be useful for a quick survey of a section before proceeding to a detailed study with the aid of much larger textbooks, or for that all important last minute review.

R.N.F.

A Textbook of Pathology: An Introduction to Medicine by William Boyd. The 7th edition, 1370 pages, illustrated. Lea & Febiger, Philadelphia.

The Macmillan Company of Canada Limited, Toronto. 1961. $18.00.

This long awaited edition of Dr. Boyd's famous textbook has finally arrived. Those who are familiar with the earlier editions will notice the obvious changes. The book has greatly enlarged in size with considerably more detail. The type is more readable now since it is set in two narrower columns rather than a single broad column. All in all it would be more appropriate to describe it as a rewritten textbook rather than a revised one.

The book is divided into two parts. Part I deals with general principles of pathology. Subjects such as inflammation, repair, neoplasia, bacterial, fungal and viral infections are discussed. In this section new chapters on immunity and hypersensitivity, derangements in body fluids, pigmentation, ionizing radiation and a fuller discussion of medical genetics are added.

Part II titled "Regional Pathology" deals with the detailed pathology of diseases affecting the different organ systems.

In an effort to link pathology as a part of a living functional human being, Dr. Boyd has opened several chapters of part I and most chapters of part II with a section that reviews briefly anatomical, physiological and biochemical facts that have a bearing on the disease in question.

In the discussion of the various diseases. Dr. Boyd mentions the main clinical manifestations by summarizing the symptoms, signs and laboratory findings.

The various historical illustrations and the occasional humorous notes make the reading a pleasure rather than an effort.

In summary, *A Textbook of Pathology* is an authorative and complete reference book and textbook suitable for medical students and also for post graduates who desire to have in their possession one of the classics in the history of medical writing.

P.A.K.

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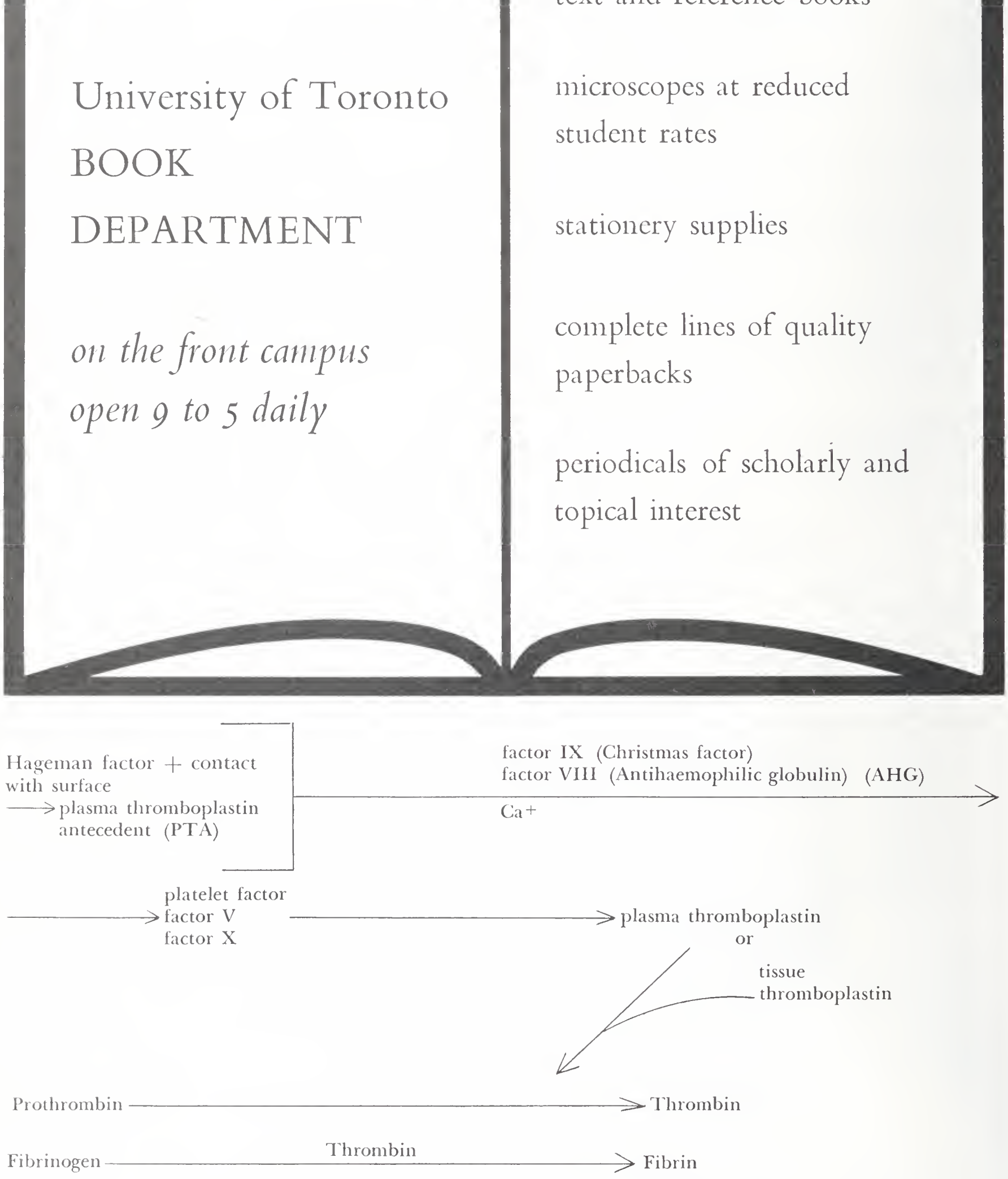

FIG. I

Oral Anticoagulants — A Review

David Naiberg 6T2

"On a Saturday afternoon in February, 1933, during a blizzard, a farmer in Wisconsin travelled over dangerous roads to visit the Agricultural Experimental Station to try and get some help because his cattle were dying in great numbers. By mistake, he went into the Biochemistry building which was Dr. Link's department and dumped on the floor a dead calf covered with hematomas, a can of blood-stained milk, and a bundle of sweet clover which was the only hay, because of the severe weather, that he had available to feed his cattle. The incident stimulated Dr. Link to consider this disease of cattle and to try and find out what caused the bleeding.

"In 1959, the Medical Research Council recommended that long term therapy with the drugs which caused this disease of cattle seemed desirable in many patients who have suffered a myocardial infarction." (1)

This review, intended primarily for the student, will acquaint him with the answers to four basic questions concerning oral anticoagulants. What? How? Why? and Where?

The first question can be answered simply. Anticoagulants are drugs which in some way decrease the tendency of the blood to clot. Bishydroxycoumarin (Dicoumarol) was the drug isolated from the spoiled sweet clover in 1940 by Dr. Link. Since then a number of chemical analogues have been produced which act similarly in depressing prothrombin activity. Five of these are coumarins — cyclocoumarin (Cumopyran), ethyl biscoumacetate (Tromexan), 4-hydroxycoumarin (Warfarin), phenprocouman (Marcumar) and acenocoumarin (Sintrom); and three are indanedione derivatives — phenylindanedione (Dindevan), 2-Diphenylacetyl-1, 3-indanedione (dipaxin) and anisindione. They are equally effective, the main difference being in the speed of their actions. It is usually recommended that the physician become well acquainted with one or two of the drugs rather than having a sketchy knowledge of all of them. The most widely used are Dicoumarol, Warfarin and phenylindanedione in Europe. The rapid acting ones show their effect in approximately 24-28 hours, whereas the slower acting ones show their maximum effect in 48-72 hours.

How Blood Clots

In the attempt to find out how anticoagulants work, many new advances in the mechanism of blood coagulation have been uncovered. In the beginning, it was thought that prothrombin was responsible for blood coagulation and that the coumarins depressed the formation of prothrombin. Quick's one stage prothrombin time test was based on the assumption that the coagulation velocity is directly proportional to the velocity of thrombin formation, which, in turn, is dependent upon the concentration of prothrombin, thromboplastin and calcium. When excess thromboplastin is added to oxalated plasma and recalcification is performed with optimal amounts of calcium, the prothrombin concentration would be the only variable, and would in turn, determine the speed of thrombin formation, and thereby the prothrombin time. The source of excess thromboplastin used in the test was a tissue extract of rabbit brain. It was believed that this brain extract provided a complete thromboplastin reagent. However, since that time, new factors have been discovered which make the picture more complicated. Owren (2) described factor V or labile factor in 1947 and one year later, Owen and Bollman (3) discovered factor VII, the stable factor. Quick's test then, was actually a measure of the amount of factors V and VII as well as the prothrombin in the plasma. The coumarins depressed factor VII rapidly, but factor V remained unaffected by them. A further piece of evidence which again threw doubts on the adequacy of the Quick test was advanced by Biggs and Douglas (4) in 1953. They showed that even in severe prothrombin lack, the one stage test was prolonged only a few seconds and, conversely, they showed that even when prothrombin is present in near normal amounts, the one stage test may be prolonged. Depression of factor VII was therefore considered to be the principal action of the coumarins and the mechanism responsible for the increased prothrombin time. In the succeeding years there was much confusion and a variety of factors, including factors IX and X, were held responsible for the action of the coumarins on blood coagulation. The present theory regards 4 factors as being influenced to a greater or lesser degree by coumarins. These are prothrombin, factor VII, factor IX and factor X. The following flow diagram shows the mechanism of blood clotting as it now stands and shows where the coumarins act. (Fig. I opposite).

Coumarins depress 2 stages of the reaction

(1) factor IX, factor X } in the production of plasma thromboplastin

(2) prothrombin, factor VII } in the production of thrombin

The production of these factors is inhibited and therefore the action is not immediately noticeable, but only after the existing supply is depleted. Similarly, after the drug is stopped, a few days are required before the prothrombin time returns to normal.

Control

For anticoagulant therapy to be considered, the full cooperation of the laboratory, the physician and the patient is required. The laboratory must have available a reliable control technique whereby the physician can know and regulate the clotting powers of his patient's blood. It is generally agreed that for a practical therapeutic level to be maintained, the prothrombin activity should be depressed to increase the prothrombin time between 2-2½ times normal. In order to keep this level reasonably constant, a number of tests have been developed which measure, more or less, the clotting time of the blood.

The first test was developed by Quick. This is the one stage or prothrombin time test which was thought to measure the concentration of prothrombin alone, and which assumed that the action of coumarins on blood coagulation was due to their action on prothrombin. Owren developed 'thrombotest', a method very sensitive to factor VII and factor IX, both of which he feels must be controlled in order to give safe treatment. He found that factor IX may be excessively reduced and haemorrhagic complications could occur even when the prothrombin time by the Quick method was within theropeutic limits.

Walker (5) agrees with Owren and feels that thrombotest is safe, practicable and easy and should be used routinely by all laboratories for the control of patients on long term anticoagulant therapy. It may well be that this means of testing will become standard in the near future. However, the majority of workers are still using the Quick one stage test because of its simplicity and universality. One defect which, if overcome, would do much to keep Quick's test as standard is the variability in the potency of the thromboplastin tissue extract. Many workers have extracts of different strengths and consequently different results are obtained. If only one standard extract was used, much confusion would be eradicated. Macmillan, Brown and Watt (6) have modified Quick's test, which takes at least ½ hour to carry out. They advocate the use of capillary blood in their determinations. The advantage to their method is that it takes less than 2 minutes to do and is therefore very good for a large outpatient clinic.

Reasons for Controversy

Before we launch into the controversy concerning anticoagulants, it might be beneficial to examine some of the reasons why differences of opinion exist. We assume that all the workers in the field are of equal intelligence and of equal good faith in carrying out their tests and reporting their results. Why, then, the differences of opinion? It is not a simple matter — many factors come into play in testing the efficacy of the drugs.

At the outset it must be emphasized that anticoagulants do not cure. They merely prevent formation and propagation of thrombi. Many patients included in the clinical trials are first started out on therapy when their disease is far advanced. The results of prophylaxis for a patient in this condition will of course be minimal. Treatment should be started early in the disease for much benefit to accrue. When these far advanced cases are included in the trials, they may give a false impression that the drug is ineffective. The proper use of controls in a large series of cases is also of utmost importance. Without a control group whose only difference from the trial group is that it does not receive therapeutic doses of anticoagulants, one cannot be sure of their value. The choice of control and treated groups must be done by unbiased random sampling. Without this, the conclusions are, of course, devaluated. The prothrombin times must be done accurately by competent personnel using a standard thromboplastin. Some series thus far reported are clouded by the disregard of these points.

Another important aspect often overlooked is strict control of prothrombin times within the therapeutic range. Everyone is sufficiently concerned over not letting the prothrombin time become too high lest haemorrhage occur, but the other side of the balance is equally as important; that is, if the prothrombin time is allowed to drop below approximately 20 seconds, not much benefit is to be expected from the treatment. Strict control, keeping the prothrombin time between 2-2½ times normal is essential.

Macmillan, Brown and Watt (7) make perhaps the most important and reasonable point concerning the controversy. They state in their discussion, that if a treatment is really effective, other workers are quick to agree on its effectiveness, whereas if the treatment is beneficial only in small degrees, it is very hard to evaluate and consequently many conflicting reports arise. It seems that this is the case with oral anticoagulants under several circumstances.

With the above facts in mind one can now go on to review the results of the trials with a more critical eye.

Indications for Anticoagulant Therapy

The indications for anticoagulant therapy are varied and certainly not settled. Each month conflicting reports are published in the journals concerning when, and when not, to use them. However, there are certain conditions in which most workers agree that their use is beneficial.

The common indications will be discussed in moderate detail, giving the results against and in favour of various workers, and only brief mention will be made of the less important indications.

Myocardial Infarction

Although a report (8) recently published in *The Lancet* finds little, if any, use for anticoagulants in the acute phase of myocardial infarction, most workers (9) still agree that they are useful. The question of long term therapy is in more doubt.

The Medical Research Council trial (10) was an extensive, well controlled survey on the effectiveness of long term anticoagulant therapy in patients who have suffered one or more previous infarctions. The results of the testing showed a marked reduction in the rate of recurrent infarction in the first year of treatment, especially in men under the age of 55 and in the high dosage group. Under 55, the reinfarction rate was reduced to about one quarter, whereas, in the over 55 year group it was reduced only to one half. It was found that there was a significant reduction in the morality rate in men under 55 in the first three to six months after infarction. Neither the reinfarction rate nor the mortality rate were significantly reduced in women. The reason for this difference is not understood.

Suzman, in Johannesberg (11), began an extensive long term anticoagulant program in 1946, using anticoagulants for chronic arteriosclerotic heart disease of all types, including angina and myocardial infarction. All of the patients in the study were treated with anticoagulants during the acute phase of myocardial infarction and then two groups were formed, one group (779 patients) continued anticoagulation on a long term basis and the second group (1111 patients) did not. He found that there were 172 deaths in the long term group as compared with 600 deaths in the short term group – a significant difference. The death rate rose with increasing age in both groups, but the rate in the short term group was significantly higher than that in the long term group. Another point of interest was that in the 291 patients who were on continuous therapy, but who discontinued their treatment after varying periods of time for one reason or another, there was a higher fatality than in those who remained on the treatment. As a result of his trials, Suzman advocates beginning anticoagulation early in the course of coronary artery disease when angina is present, and before the patient has suffered his first coronary attack. He finds that anginal patients receiving continuous anticoagulation usually improve and may even be relieved of their symptoms within a few months time.

On the other hand, some workers find little, if any, benefit from long term anticoagulation. Macmillan, Brown and Watt (8), in Toronto, conducted a survey using the same conditions as did the M.R.C. of Great Britain, the only difference being the use of their modification of the Quick one stage test using capillary blood, and the use of Dicoumarol rather than phenylindanedione. In their preliminary report they found that Dicoumarol used on a long term basis failed to protect their patients from further myocardial infarction and also failed to reduce the mortality rate. On the contrary, there were more deaths in the high treatment group than in the low treatment group. There were 8 deaths in 27 patients on therapy and no deaths in the control group. There were 4 reinfarctions in the low dosage group as compared with 6 in the high dosage group. They also observed a considerable rate of haemorrhagic complications – 8 to 1.

It would seem that the current status of long term anticoagulant therapy in relation to myocardial infarction is, for the most part, as yet unsettled. The results of most testing to date, however, would seem to indicate that they are of use in men under 55 years of age, especially within the first 6 months to a year after infarction.

Thromboembolism and Cerebrovascular Disease

There are still many differences of opinion concerning the use of oral anticoagulants in cere-

brovascular disease. The reasons for this are obvious. The type of cerebrovascular disease is difficult to diagnose — is it haemorrhage or thrombosis? Also our knowledge of the natural history of the disease leaves much to be desired.

Millikan (12) has classified strokes into three categories and advocates the use of anticoagulants only in certain sharply demarcated instances.

Incipient or impending stroke. The patient has intermittent insufficiency in either the vertebral-basilar or carotid systems. These attacks last for a matter of minutes and then disappear, leaving no residual damage. In a study of 115 patients on therapy and 115 patients not on therapy, the symptoms disappeared in 80% of the patients on therapy, whereas in the non treatment group only 30% stopped having attacks (clearing up spontaneously). Significantly too, about one third of the non treatment patients sustained serious cerebral infarctions, whereas only 3.5% of the anticoagulant group were similarly afflicted. Intracerebral haemorrhage was not significant. Millikan thinks that patients having one, two or even three attacks should not be treated, but treatment should be instituted immediately in those patients whose attacks are of increasing frequency and severity.

Advancing stroke. Here there is active progression of the neurologic deficit over a period of minutes or hours occuring during the period of observation. This can occur in both systems and is probably due to actively advancing cerebral thrombosis. In the vertebral-basilar system it was found that out of 140 patients on the treatment, only twelve died, whereas in a group of 39 patients not on treatment, 23 died — an impressive result.

Actively advancing thrombosis in the carotid system, while not enough cases were studied to be conclusive, showed a similar trend. Anticoagulants should be used.

Completed strokes. Here there is a stable neurological deficit. Theoretically, treatment here would be useless because the area of irreversible brain damage is no longer able to function. The data accumulating about this is generally in agreement, although there are some differences of opinion.

Anticoagulants are being used successfully in the treatment of recurrent arterial embolism. In a ten year experience, McDevitt (13) *et al.* found anticoagulant therapy to be effective in reducing the incidence of recurrent thromboembolic episodes due to various primary conditions such as rheumatic heart disease, arteriosclerotic heart disease and auricular fibrillation. A total of 229 thromboembolic episodes occurred during 2,842 patient-months in the non-treatment control group whereas only 72 episodes occurred during 2,291 patient-months in the treatment group.

Wright (14) agrees that it is logical to give anticoagulants to patients suffering from cerebral emboli arising from both fibrillating and non-fibrillating hearts to prevent further embolism, and to prevent extention of the clot which is already lodged in the cerebral artery. A problem which still exists however, is the question of whether an embolic infarct is made into a haemorrhagic infarct by the administration of anticoagulants. If this occurs, the infarcted area is increased and the patient is, of course, worse. Further studies along these lines would be beneficial.

Marshall (15), in a paper presented before the Symposium on Anticoagulant Therapy at the Royal Society of Medicine in November of 1960, reported that the use of anticoagulants in a group of patients with acute, non-embolic, cerebral infarction did not improve the outcome when compared with the group of patients who did not receive the drugs. He also found that the use of anticoagulants on a long term basis did not benefit these patients. On the contrary, the risk of haemorrhage was great enough to be prohibitive. He feels that as a practical therapeutic measure, anticoagulants are not feasible due to the difficulty in diagnosis of the type of cerebrovascular attack in the acute phase. Thrombosis may be confused with haemorrhage and the risk of further haemorrhage is thus increased. In order to help overcome this difficulty in diagnosis, a lumbar puncture should be done on all such patients. Anticoagulants should never be given until after the puncture has revealed a clear, colourless cerebrospinal fluid.

Peripheral Arterial Disease

Richards (16) in Glasgow has considered the indications for anticoagulants in peripheral arterial disease in two main groups. (a) Acute Arterial Occlusion, (b) Chronic Arterial Occlusion.

Acute Arterial Occlusion. This occurs usually by embolism and occasionally by thrombosis. Although there may be some difficulty in differentiating between these two types of occlusions, especially if an obvious source of embolism is absent, the immediate treatment is fortunately the same. If seen within the first hour or two, medical mangement including anticoagulants is usually begun with intravenous herapin. If all goes well, the patient should be given oral anticoagulants

after about ten days. If the patient is first seen after six to eight hours, or if the limb otherwise deteriorates, embolectomy or thrombectomy should be considered. If the occlusion is embolic, anticoagulants will reduce the risk of further embolism. Owren (17) has substantiated this conclusion by showing that in a group of 60 treat ment years there were no embolic episodes, whereas in a control group of 81 observation years, there were no less than 22 recurrent major embolic episodes.

The question of using anticoagulants in acute thrombosis (no source of embolism) remains unsettled. It is suggested that they be used for about a two year period following the accident.

An acute episode may also occur in an artery already damaged by obliterative arterial disease. Here the best treatment is to start anticoagulant treatment immediately with heparin and continue in 48 hours with oral anticoagulants. Richards feels here, however, that the patient with obliterative arterial disease should be taking prophylactic anticoagulants before an acute attack has a chance to occur.

Chronic Arterial Occlusion. Patients with intermittent claudication (the commonest chronic arterial occlusive disease) seem to have a high incidence of acute occlusion of the major arteries of the lower limbs and on this basis, he feels that all patients with intermittent claudication should receive long term pophylactic anticoagulants. He thinks that people with progressive ischaemia (obliterative arterial disease which is becoming worse rapidly) and people with thromboangiitis obliterans might benefit from anticoagulants as well.

Angina Pectoris

When new drugs such as these are made available, they are often, in the early stages of evaluation, hailed as a panacea to be used in a wide variety of diseases. Such is the case with oral anticoagulants. Some reports already published are not only enthusiastic about their effect in decreasing the incidence of reinfarction and the mortality rate, but also claim that the anticoagulants actually decrease existing angina (18). The reason for this is unknown and can only be explained by some unknown mechanism the anticoagulants may have in dissolving the existing occlusion to some extent.

One study found (19) that on long term anticoagulant therapy, the observed mortality rate in anginal patients was 3.6% per year, which is down from the expected 6-10% per year in non-treated patients.

Borchgrevink (20) reports that he found a five-fold reduction in the reinfarction rate and a seven-fold reduction in the mortality rate in anginal patients on continuous anticoagulant therapy. He advocates the use of long term anticoagulants in all patients with angina, regardless of whether or not they have suffered a previous myocardial infarction.

Wright (14) is not as enthusiastic about the value of anticoagulants in angina because of the difficulty in assessing angina. It is a subjective symptom and as such is regarded differently by different people. Although it is his impression that they are of some use in preventing an infarction, he stresses that statistical data are difficult to formulate from subjective symptoms.

In spite of this, the majority of workers are against the routine use of anticoagulants in angina. More work is needed along these lines.

Prophylaxis in Postoperative Patients

Sevitt (21) ran a trial to find out whether anticoagulants reduce venous thrombosis and pulmonary embolism in injured patients. As subjects he chose elderly patients with fractured hips (who ordinarily have a high incidence of venous thrombosis and embolism) and divided them into two groups. 150 patients received phenindione therapy to prolong the Quick prothrombin time to between 2-3 times normal and 150 patients did not receive anticoagulant therapy. Embolism did not occur in any patient under treatment, but there was an 18% rate of embolism in the control group, 10% being fatal. There were 4 cases of venous thrombosis in the treated group as compared with 43 cases in the control group. As a result of his study, Sevitt recommends using anticoagulants prophylactically in persons over 45 years of age who are about to undergo a period of bedrest for over 2-3 days, and in whom there are no contraindications.

Belding (22) in California agrees that the drugs should be used prophylactically on the basis of a 0.93% postoperative thrombophlebitis rate in the untreated group as compared with a 0.13% incidence in the treated group.

Some Important Points

Dosages and Control

The usual dose of Dicoumarol is 300 mgm. the first day, 200 mgm. the second day, 100 mgm. the

third day, and anywhere from 25-100 mgm. each day as maintenance therapy, depending on the result of the prothrombin times. The optimum response is the prolongation of the prothrombin time to between 2 to 2½ times normal. Within these limits, anticoagulants are reasonably safe, whereas if the prothrombin is greater than 2½ times normal, haemorrhagic episodes occur more frequently. If the prothrombin time is less than twice normal, little therapeutic effect can be expected.

In order for a patient to be well controlled, he should be stabilized while in hospital and his maintenance dose regulated. Following discharge from hospital, he should have regular prothrombin time tests at three week intervals, depending on the stability of his prothrombin time.

If bleeding should occur, he should receive vitamin K_1, phytonadione (Mephyton®) immediately. If the haemorrhage is very severe, 50 mgm. of Mephyton intravenously is indicated. If the haemorrhage is moderate, one or two 5 mgm. tablets should be given orally until the prothrombin time is down to therapeutic levels. If the haemorrhage is minor (minor epistaxis or a few red cells in the urine) merely a cessation of treatment will decrease the prothrombin time to within safe limits.

Terminating Therapy

Some physicians (23) (24) feel that anticoagulants should be continued indefinitely because of the risk involved in their termination. They have described a "rebound phenomenon" when treatment is stopped, resulting in new thromboembolic episodes. This was thought to be due to an increased clotting tendency. Wright (14) thinks that this is false and attributes it to a "catching up" phenomenon. He sees the atherosclerotic process as continuing during therapy, but that it prevents thrombosis from closing off the arteries. When anticoagulants are stopped, thrombosis occurs in the narrowed vessels easily, thus giving rise to a false impression of rebound.

Contraindications

As with any drug, there are certain contraindications to the use of anticoagulants. These are dangerous drugs to use if the patient is not careful. Haemorrhage may occur and may prove fatal. For this reason, anticoagulants should be given only to patients who can be made to understand that regular blood testing is essential and that the drugs must be taken regularly. They must be warned that intercurrent infections can prolong the prothrombin time of the blood, especially so if they do not eat and if broad spectrum antibiotics are being taken. Similarly, patients in heart failure must be very careful to have their blood tested regularly. Drugs such as aspirin, phenylbutazone, and steroid hormones are also contraindicated during anticoagulant therapy. Peptic ulceration and any bleeding disorder are contraindications to anticoagulants, lest a severe haemorrhage occur.

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ABSTRACT: *Current Views About Seat Belts*: Editorials and Comments, The Canadian Medical Association Journal, Vol. 85, No. 6, Aug. 5, 1961, pp. 312-313.

In one study it was found that those who used seat belts sustained 35% fewer "major-to-fatal" injuries than non-users. The rate for "any injury" was about the same in both groups. The seat belts offered little protection in front-front and front-rear accidents (the total of which constitute about 33% of accidents), whereas in rollover (20% of accidents) and angled impact accidents (about 47% of accidents), the observed total of "major-to-fatal" injuries in belt users was less than half of that in the group without belts.

In a recent survey in the U.S.A. it was estimated that less than 1% of automobile operators had safety belts installed in their vehicles. In 2000 belt equipped cars that were involved in collisions, the seat belts were not in use in almost 70% at the time of the accident. Seat belts are required for local driving. The risk of "local hops" is reflected in the fact that in 1958, 47% of all deaths occurred at travel speeds below 40 mph. and 66% took place within 25 miles of the driver's home.

D. S.

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On Inspection

Answers to Questions from page – 20

Fig. 1 – Lingual Thyroid

This anomaly represents the persistence of part or all of the thyroid gland in its point of origin at the foramen caecum. Present from birth, the mass tends to enlarge at puberty, during pregnancy, and at the menopause. It must be differentiated from a thyroglossal duct cyst which presents as a firm round swelling, averaging 1-2 cm. in diameter, as opposed to the lingual thyroid, which is softer, less well circumscribed, and may have a tendency to bleed from trauma and ulceration.

Symptoms are difficulty in speaking, swallowing, or breathing, and a desire to swallow continuously. They are all due to the swelling at the base of the tongue.

Treatment is witheld if there is no thyroid tissue in its normal position and symptoms are tolerable; or, in the presence of normally located thyroid tissue as well as the lingual thyroid, surgical removal is indicated.

The chief complication is myxoedema. This arises when there has been complete failure of descent of the thyroid and the lingual mass, consisting of all the thyroid tissue in the body, is removed surgically.

Fig. 2 – Hodgkins Disease

Diagnosis was confirmed by biopsy of the left supraclavicular mass.

Enlargement of the left supraclavicular node may result from infection in the thumb, index finger, or neck. If the right node is enlarged, a primary lesion in the chest should be suspected; but if it be the left node that is involved, then the abdomen must be carefully checked for a primary process.

The various forms of treatment presently used are as follows:

(1) Radical surgical excision – when the disease has been diagnosed early enough and is still localized.
(2) Segmental or localized irradiation – rather than total irradiation, unless generalized dissemination of the disease has occurred.
(3) Chemotherapy – e.g. nitrogen mustard.
(4) A combination of the above.

This patient received courses of irradiation and nitrogen mustard with little remission of his disease. A course of vincoleukoblastine (VLB) recently tried in his case caused marked decrease in size of scapular, chest wall, and axillary masses.

The pneumothorax was considered to be unassociated and was left in as a red herring!

Fig. 3 – Gouty Arthritis

This gentleman had been suffering from gout for approximately thirty years. Thus one should be tempted to call his a case of chronic gout, a diagnosis which can be made after a patient has had recurrent acute attacks of gout, culminating in deformity of joints. Urates are deposited in joint spaces, capsules, tendons, bursae, and skin. Often, in cases this advanced, sinuses develop which drain chalky white material and many joints may be ankylosed.

This patient had tophi all over his body, including face, sternum, spine, feet, knees, and elbows. However he had no history of urinary calculi, one of the complications of this disease.

Other complications which may be encountered are:

(1) Slowly progressive renal impairment with azotaemia, resulting in death before age fifty.
(2) Hypertensive cardiovascular disease of the benign variety with generalized arteriosclerosis.
(3) Muscular atrophy, chiefly due to disuse of deformed joints.
(4) Crippling.

Fig. 4 – Horner's Syndrome

Meiosis of the pupil, ptosis of the eyelid, enopthalmos, and abolition of sweating over one side of the face constitute Horner's Syndrome (also called Bernard-Horner's Syndrome).

Essentially, the lesion is a disruption of the sympathetic supply to one side of the face (in this case the right side). The lesions themselves that can produce this are varied:

(1) Section of the cervical sympathetic fibres in the neck or at any point along the internal carotid arteries (postganglionic fibres)
(2) Removal of the superior cervical ganglions
(3) Interruption of preganglionic fibres from

the eighth cervical and first through third thoracic segments

(4) Interruption of the descending uncrossed hypothalamospinal pathway in the lateral tegmentum of medulla or cervical cord.

These lesions may in turn be caused by neoplastic or inflammatory involvement of cervical lymph nodes, neoplastic invasion of the proximal part of the brachial plexus, surgical trauma in operations on neck structures, basal skull fractures, brain or cord tumours, syringomyelia, or traumatic lesions of the first and second thoracic spinal segments.

The iris on the side of the lesion fails to become pigmented and may remain blue or mottled gray-brown and blue if the syndrome develops in early life.

Fig. 5 — Felty's Syndrome

The triad of febrile migratory polyarthritis, splenomegaly and leukopaenia was first described in 1924 by Felty as having occurred in five of his patients. Since that time, many more cases presenting with this triad have been discovered, and consequently the syndrome has borne Felty's name.

Many feel that this syndrome is merely a variant of rheumatoid arthritis, but there is a possibility that some of the patients had rheumatoid arthritis with unassociated hypersplenism. Others may have had systemic lupus erythematosus.

Figs. 6 and 7 — Ewing's Sarcoma

Two years prior to his death, this young man suffered trauma to his right knee followed by prolonged pain and swelling, but no fracture was seen on radiological examination. Seven months prior to death he was first admitted to hospital with a pathological fracture of the tumour site at the proximal end of the tibia. A biopsy was performed. Two months prior to his demise the patient was highly anaemic (3G.) but the white cell count was still in the normal range. Subsequently, the latter progressed gradually to low values. At this time, his right lower leg was diffusely swollen with slight redness and heat at the proximal end of the tibia, plus hardening and nodularity of the overlying skin at this site.

In the right inguinal region there was a bony hard solid mass, 4 cm. in diameter, with considerable fixation. Also, in the right temporoparietal area, there was a large solid mass 5 cm. in diameter which was slightly tender to palpation. The lungs appeared clear.

The patient was not in acute distress, his tongue was dry and there was a foul odour from his mouth. His weight remained fairly stable. His temperature rose to 101° and 102°.

Differential Diagnosis. 1. Osteosarcoma.
2. Ewing's sarcoma.
3. Primary reticulum cell sarcoma of bone.
4. Chondrosarcoma.
5. Fibrosarcoma.
6. Metastatic neuroblastoma.

Pathologic Diagnosis. Ewing's sarcoma.

ABSTRACT: *Etiology of Cat Scratch Fever*: Gladys L. Boyd, M.D. and Grace Craig, R.T.: The Journal of Pediatrics, Vol. 59, Sept. 1961.

Cat scratch fever has been thought to be caused by psittacosis virus, cats being the purveyors from a pool in nature, with birds as the possible carriers. Recent world-wide studies have shown the presence of T.B. sensitizing atypical acid fast bacilli in fields and grasses, which give a low grade T.B. sensitivity in animals and man.

The lygranum skin test is not reliable. Other viral studies have been inconclusive. In the past few years the authors have found an increasing number of atypical acid fast organisms in lymph nodes, urine and gastric washings of patients which, on smear, could not be differentiated from T.B. bacilli but which, on culture, proved to be atypical acid fast bacilli of a chromogen group. In cat scratch fever they were invariably of one type.

The results of enzyme studies, animal inoculation and drug sensitivity tests corroborated the culture findings.

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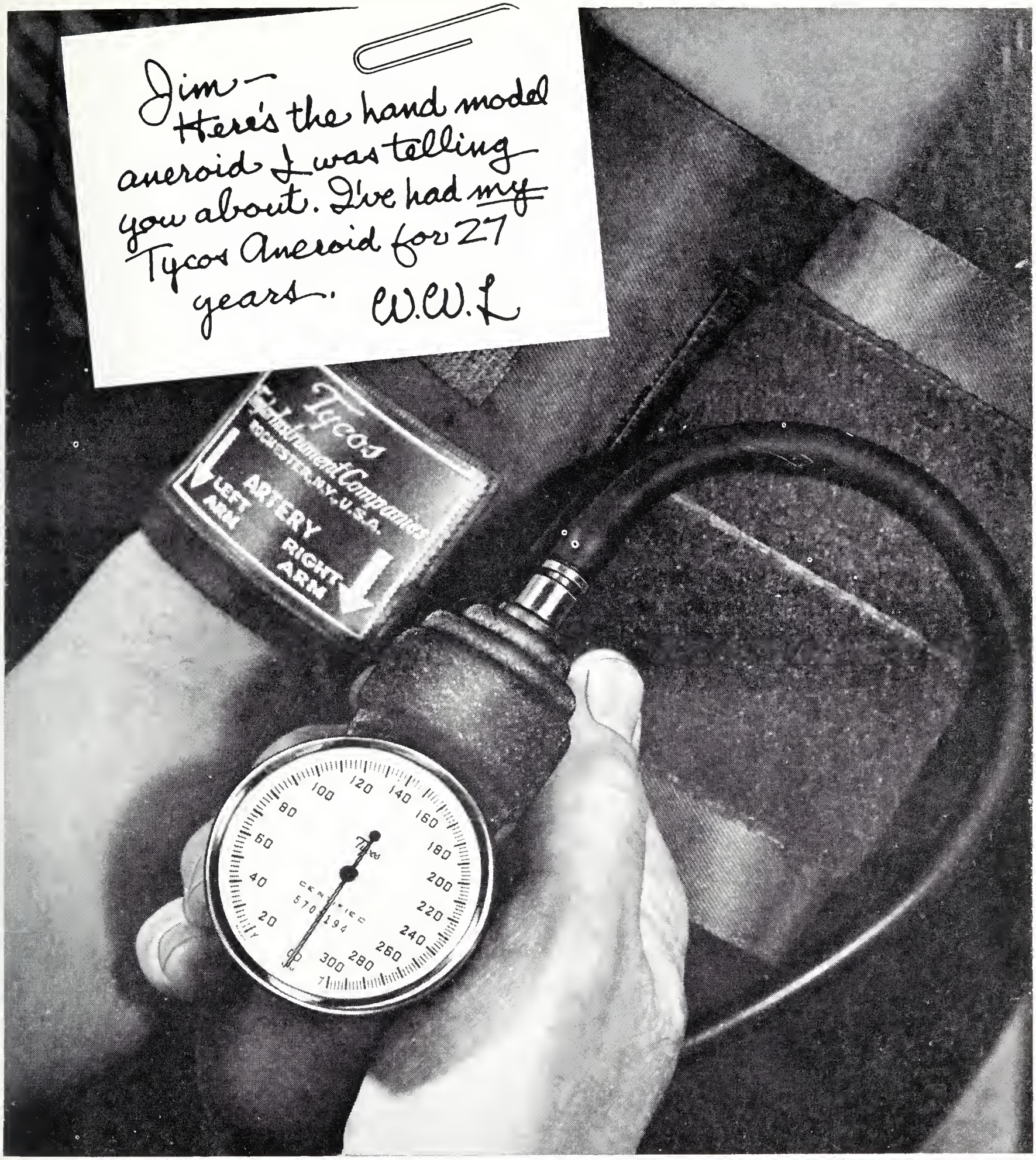

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